

Supplementary data for article:

Božinović, N. S.; Opsenica, I.; Šolaja, B. A. Double Palladium-Catalyzed Synthesis of Azepines.  
*Synlett* **2013**, 24 (1), 49–52. <https://doi.org/10.1055/s-0032-1317667>

Supporting Information  
for DOI: 10.1055/s-0032-1317667  
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## Supporting Information

### Double Palladium Catalyzed Synthesis of Azepines

Nina Božinović, Igor Opsenica, Bogdan A Šolaja\*

*Faculty of Chemistry, University of Belgrade, PO Box 51,  
Studentski trg 16, 11158 Belgrade, Serbia*

bsolaja@chem.bg.ac.rs

#### Supporting Information Contents:

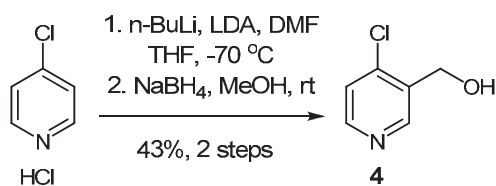
##### 1) General Information

##### 2) Experimental Procedures and Characterization Data for Products

##### 3) <sup>1</sup>H NMR and <sup>13</sup>C NMR Copies of Products

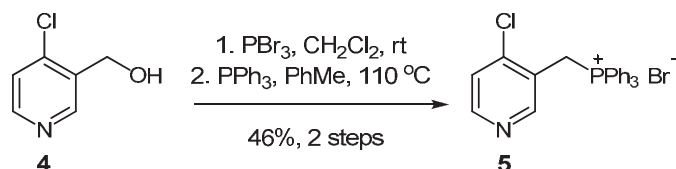
##### 4) References

**General Information:** 4-Chloropyridine hydrochloride was purchased from Fluka. Manganese(IV)-oxide was purchased from Merck. Other chemicals were purchased from Aldrich. Microwave reactions were performed in a Biotage Initiator 2.5 microwave reactor. Melting points were determined using a Boetius PMHK apparatus (Carl Zeiss, Germany) and were not corrected. IR spectra were recorded on a Perkin-Elmer spectrophotometer FTIR 1725X. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Varian Gemini-200 spectrometer (at 200 and 50 MHz, respectively), and a Bruker Ultrashield Advance III spectrometer (at 500 and 125 MHz, respectively) employing indicated solvents (*vide infra*) using TMS as the internal standard. Chemical shifts are expressed in ppm (δ) values and coupling constants (*J*) in Hz. ESI-MS (HRMS) spectra of the synthesized compounds were acquired on a Agilent Technologies 1200 Series instrument equipped with a Zorbax Eclipse Plus C18 (100 × 2.1 mm i.d. 1.8 μm) column and DAD detector (190-450 nm) in combination with a 6210 Time-of-Flight LC/MS instrument in positive ion mode. The samples were dissolved in pure MeOH (HPLC grade). The selected values were as follows: capillary voltage = 2.5 kV, gas temperature = 250 °C, drying gas = 7 L min<sup>-1</sup>, nebulizer pressure = 30 psig, and fragmentator voltage = 50 V. GC/MS spectra of the synthesized compounds were acquired on a Agilent Technologies 7890A equipped with a DB-5 MS (30 m × 0.25 mm × 0.25 μm) column and 5975C MSD and FID detector. The selected values were as follows: carrier gas was He (1.0 mL/min), temperature linearly increased 40-315 °C (10 °C/min), injection volume = 1 μL, temperature = 250 °C, temperature (FID detector) = 300 °C, and EI mass spectra range: 40-550 m/z. Lobar LichroPrep Si 60 (40-63 μm) or LichroPrep RP-18 columns (Merck, Germany), coupled to a Waters RI 401 detector, were used for preparative column chromatography. Thin-layer chromatography was performed on pre-coated Merck silica gel 60 F254 and Merck RP-18 F254 plates. The solution MeOH (NH<sub>3</sub>) stands for combination MeOH/NH<sub>3</sub> aq = 9:1, and the solution CH<sub>2</sub>Cl<sub>2</sub> (PhMe) corresponds to CH<sub>2</sub>Cl<sub>2</sub>/PhMe = 99:1.



#### 4-Chloropyridine-3-methanol (4).<sup>1</sup>

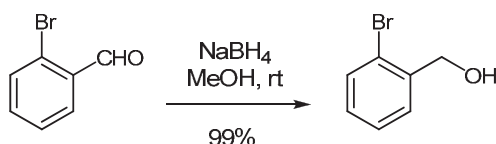
To a solution of  $i\text{Pr}_2\text{NH}$  (0.670 mL, 4.78 mmol) in THF (2.0 mL) 1.6 M  $n\text{-BuLi}$  in hexane (2.43 mL, 3.90 mmol) was added dropwise at  $-78\text{ }^\circ\text{C}$  under Ar. After stirring for 5 min at  $0\text{ }^\circ\text{C}$  the mixture was cooled to  $-78\text{ }^\circ\text{C}$  and used in the next reaction. To a suspension of 4-chloropyridine hydrochloride (500 mg, 3.33 mmol) in dry THF (5 mL) 1.6 M  $n\text{-BuLi}$  in hexane (2.10 mL, 3.33 mmol) was added dropwise at  $0\text{ }^\circ\text{C}$  under Ar. After stirring at room temperature for 30 min the reaction was cooled to  $-78\text{ }^\circ\text{C}$  and prepared LDA solution was added. Upon stirring at the same temperature for 30 min DMF (380  $\mu\text{L}$ , 4.95 mmol) was added. The reaction was warmed to room temperature gradually and stirred overnight. It was quenched with 3 M HCl and resulting mixture was stirred for 2 h at r.t. The solution was neutralized with  $\text{NaHCO}_3$ , it was extracted with  $\text{CH}_2\text{Cl}_2$ , dried over  $\text{Na}_2\text{SO}_4$ , and evaporated to give crude aldehyde as brown oil. The obtained aldehyde was dissolved into MeOH (25 mL), and  $\text{NaBH}_4$  (187 mg, 4.95 mmol) was added to the solution. After stirring for 3 h at room temperature, the reaction was concentrated. Water was added to the residue, and extracted with  $\text{CH}_2\text{Cl}_2$ , followed by drying over anh.  $\text{Na}_2\text{SO}_4$ , and evaporation to dryness. Column chromatography using hexane/EtOAc = 8:2 afforded desired compound **4** as pale yellow powder (206 mg, 43%), mp =  $87\text{--}90\text{ }^\circ\text{C}$ .  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  8.65 (s, 1H), 8.37 (d,  $J = 5.6$  Hz, 1H), 7.30 (d,  $J = 5.6$  Hz, 1H), 4.82 (s, 2H), 4.43 (s, 1H).  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  149.4, 149.1, 143.0, 134.8, 124.4, 60.0. IR (ATR): 3176, 2925, 2853, 1582, 1563, 1468, 1443, 1405, 1359, 1226, 1190, 1067, 830, 715  $\text{cm}^{-1}$ . (+)ESI-HRMS ( $m/z$ ):  $[\text{M} + \text{H}]^+$  144.02063 (error -3.01 ppm).



#### [(2-Chloropyridine-3-yl)methyl](triphenyl)phosphonium bromide (5).

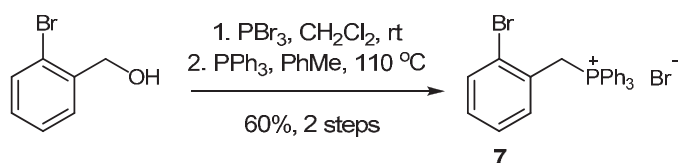
To a solution of alcohol **4** (0.80 g, 5.6 mmol) in  $\text{CH}_2\text{Cl}_2$  (45 mL)  $\text{PBr}_3$  (1.0 mL, 11 mmol) was added. After stirring for 2 h at room temperature the reaction mixture was cooled to  $0\text{ }^\circ\text{C}$  it was neutralized with  $\text{NaHCO}_3$ , extracted with  $\text{CH}_2\text{Cl}_2$ , dried over  $\text{Na}_2\text{SO}_4$ , and evaporated to dryness. Column chromatography using hexane/EtOAc = 1:1 afforded product as red oil. Obtained intermediate was dissolved in PhMe (18 mL) and  $\text{PPh}_3$  (1.5 g, 5.9 mmol) was added. Resulting reaction mixture was refluxed for 6 days. After cooling to room temperature, product was filtered, washed with diethyl ether and dried under reduced pressure at  $45\text{ }^\circ\text{C}$ . Desired phosphonium bromide was obtained as white powder (1.2 g, 46%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.69 (s, 1H), 8.41 (s, 1H), 7.88–7.60 (m, 15H), 7.20–7.13 (m, 1H), 5.84 (d,  $J = 14.5$  Hz, 2H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  153.1 (d,  $J = 5.5$  Hz), 150.4 (d,  $J = 3.6$  Hz), 145.6 (d,  $J = 5.5$  Hz), 135.4 (d,  $J = 2.6$  Hz), 134.2 (d,  $J = 10.0$  Hz), 130.4 (d,  $J = 12.5$  Hz), 124.3, 123.3, 117.1 (d,  $J = 84.8$  Hz), 26.2 (d,  $J = 49.6$  Hz). IR (ATR): 2998, 2861, 2838, 2769, 1644, 1556, 1481, 1435, 1402, 1319, 1191, 1159, 1107, 995, 855, 751, 725, 692  $\text{cm}^{-1}$ .

<sup>1</sup> Takano, Y.; Shiga, F.; Asano, J.; Ando, N.; Uchiki, H.; Fukuchi, K.; Anraku, T. *Bioorg. Med. Chem.* **2005**, *13*, 5841.



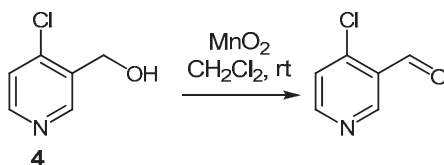
#### (2-Bromophenyl)methanol.

2-Bromobenzaldehyde (1.26 mL, 10.8 mmol) was dissolved in MeOH (25 mL), and NaBH<sub>4</sub> (491 mg, 12.9 mmol) was added to the solution. After stirring for 18 h at room temperature, the reaction mixture was concentrated. Water was added to the residue and the product was extracted with CH<sub>2</sub>Cl<sub>2</sub>, organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated. The desired product was obtained as pale yellow oil (2.00 g, 99%) and was used without any further purifications. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ 7.58-7.42 (m, 2H), 7.38-7.24 (m, 1H), 7.22-7.10 (m, 1H), 4.72 (s, 2H), 2.31 (s, 1H). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ 139.7, 132.6, 129.1, 128.8, 127.6, 122.5, 65.0. GC-MS (*m/z* (%)): 186.0 ([M]<sup>+</sup> (43)), 169.0 (5), 157.0 (10), 107.1 (70), 89.1 (11), 79.0 (100). IR (ATR): 3992, 3970, 3912, 3892, 3857, 3304, 3078, 2910, 2858, 2710, 2577, 2029, 1965, 1567, 1466, 1439, 1364, 1264, 1244, 1196, 1113, 1056, 1021, 989, 939, 798 cm<sup>-1</sup>.



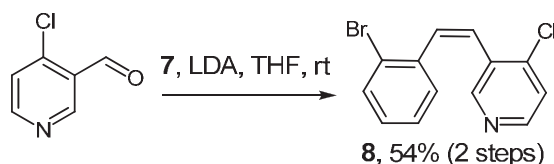
#### [(2-Bromophenyl)methyl](triphenyl)phosphonium bromide (7).

(2-Bromophenyl)methanol (2.00 g, 10.7 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL), and PBr<sub>3</sub> (2.00 mL, 21.3 mmol) was added. After stirring for 2 h at room temperature resulting reaction mixture was cooled to 0 °C, neutralized with NaHCO<sub>3</sub>, extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated to dryness. Column chromatography using hexane/EtOAc = 8:2 afforded product as pale red oil 1.70 g. Product was dissolved in PhMe (75 mL) followed by addition of PPh<sub>3</sub> (1.97 g, 7.62 mmol). Resulting reaction mixture was refluxed for 6 days. After cooling to room temperature, product was filtered off, washed well with diethyl ether and dried under reduced pressure at 45 °C. Phosphonium salt **7** was obtained as white powder, 3.30 g (60%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.80-7.72 (m, 3H), 7.65-7.56 (m, 12H), 7.49-7.44 (m, 1H), 7.35-7.30 (m, 1H), 7.14-7.06 (m, 2H), 5.52 (d, *J* = 14.5 Hz, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 135.1 (d, *J* = 2.7 Hz), 134.1 (d, *J* = 10.0 Hz), 132.8, 132.8, 130.1 (d, *J* = 12.6 Hz), 128.2 (d, *J* = 3.5 Hz), 127.4 (d, *J* = 9.1 Hz), 127.0 (d, *J* = 7.2 Hz), 116.9 (d, *J* = 84.9 Hz), 30.8 (d, *J* = 48.8 Hz). IR (ATR): 3038, 3015, 2984, 2941, 2855, 2773, 2689, 1585, 1475, 1437, 1401, 1321, 1273, 1190, 1160, 1108, 1028, 995, 829, 784, 756, 723 cm<sup>-1</sup>.



#### 4-Chloropyridine-3-carbaldehyde.

Alcohol **4** (92 mg, 0.65 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) followed by addition of MnO<sub>2</sub> (0.56 g, 6.5 mmol). After stirring for 2 h at room temperature reaction mixture was filtered and solvent was evaporated to dryness. The obtained 4-chloropyridine-3-carbaldehyde was found to be unstable, and consequently was used in the next reaction without further purification.

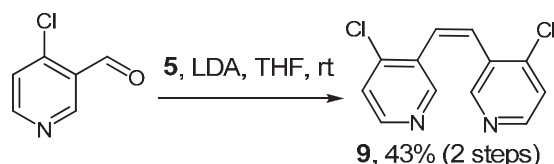


### 1,3'-(*Z*)-Ethene-1,2-diyl-1-(2-bromobenzene)-2-(4-chloropyridine) (**8**).

To a suspension of phosphonium salt **7** (338 mg, 0.660 mmol) in THF (5 mL) was added prepared LDA (0.40 mL, 0.78 mmol). After 30 min 4-chloropyridine-3-carbaldehyde (92 mg, 0.65 mmol) dissolved in THF (1 mL) was added over 5 min. The reaction mixture was stirred at room temperature and after 16 h it was quenched with NaHCO<sub>3</sub>. The aqueous phase was separated and extracted with EtOAc (3 × 10 mL). The organic extracts were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuum and purified by column chromatography (RP, CH<sub>2</sub>Cl<sub>2</sub> (PhMe)/MeOH = 7:3) to yield (*Z*)-**8** (104 mg, 54%), and (*E*)-**8** (24 mg, 12%).

(*Z*)-**8**: light yellow solid, mp 40-41 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.29 (d, *J* = 5.3 Hz, 1H), 8.16 (s, 1H), 7.61-7.56 (m, 1H), 7.31 (d, *J* = 5.3 Hz, 1H), 7.12-7.03 (m, 2H), 6.98-6.90 (m, 1H), 6.93 (d, *J* = 12.0 Hz, 1H) 6.75 (d, *J* = 12.0 Hz, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 151.2, 148.7, 143.2, 136.4, 133.4, 132.9, 131.5, 130.4, 129.2, 127.2, 124.8, 124.2, 123.9. IR (ATR): 3084, 3057, 3031, 1572, 1544, 1459, 1400, 1076, 1044, 961, 820, 789, 751, 691 cm<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M + H]<sup>+</sup> 293.96877 (error 2.73 ppm).

(*E*)-**8**: white solid, mp = 46-48 °C <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.92 (s, 1H), 8.40 (d, *J* = 5.3 Hz, 1H), 7.71 (dd, *J* = 7.8 Hz, *J* = 1.4 Hz, 1H), 7.62 (dd, *J* = 8.0 Hz, *J* = 0.9 Hz, 1H), 7.56 (d, *J* = 16.0 Hz, 1H), 7.38-7.33 (m, 2H), 7.30 (d, *J* = 16.0 Hz, 1H), 7.22-7.16 (m, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 149.0, 148.3, 142.4, 136.3, 133.2, 131.7, 131.5, 129.7, 127.6, 127.1, 124.5, 124.4, 124.1. IR (ATR): 3059, 2931, 2856, 1632, 1568, 1544, 1469, 1432, 1402, 1323, 1281, 1220, 1117, 1074, 1022, 958, 816, 750 cm<sup>-1</sup>. GC-MS, RT 24.00 min (*m/z* (%)): 294.9 ([M]<sup>+</sup> (100)), 214.0 (78), 179.0 (74), 151.0 (67), 126.0 (14), 107.0 (17), 89.0 (12), 76.0 (29), 63.0 (15), 51.0 (9). (+)ESI-HRMS (*m/z*): [M + H]<sup>+</sup> 293.96765 (error -1.09 ppm).



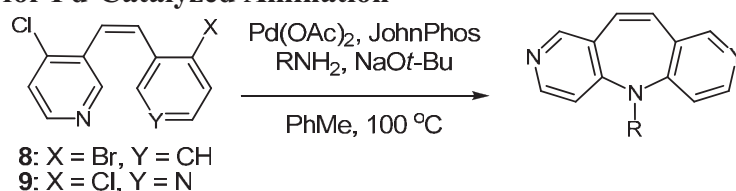
### 3,3'-(*Z*)-Ethene-1,2-diylbis(4-chloropyridine) (**9**).

The phosphonium salt **5** (1.0 g, 2.1 mmol) and 4-chloropyridine-3-carbaldehyde (0.30 g, 2.1 mmol) were transformed into (*Z*)-**9** (0.23 g, 43%), and (*E*)-**9** (12 mg, 2%) using freshly prepared LDA (2.0 mL, 4.0 mmol). The crude products were purified using preparative column chromatography (SiO<sub>2</sub>, hexane/EtOAc = 8:2).

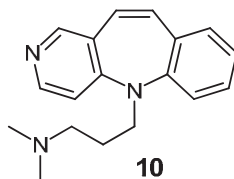
(*Z*)-**9**: light yellow powder, mp 130-131 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.34 (d, *J* = 5.5 Hz, 1H), 8.14 (s, 1H), 7.34 (d, *J* = 5.5 Hz, 1H), 6.90 (s, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 150.7, 149.4, 143.4, 131.2, 127.6, 124.5. IR (KBr): 3431, 3041, 2928, 2856, 1631, 1571, 1550, 1463, 1401, 1301, 1219, 1193, 1075, 972, 870, 816 cm<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M + 2H]<sup>2+</sup> 126.00988 (error -4.92 ppm), [M + H]<sup>+</sup> 251.01382 (error 0.38 ppm).

(*E*)-**9**: white solid, mp = 127-129 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.91 (s, 1H), 8.44 (d, *J* = 5.5 Hz, 1H), 7.45 (s, 1H), 7.37 (dd, *J* = 5.5 Hz, *J* = 0.5 Hz, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 149.6, 148.3, 142.8, 131.1, 125.9, 124.6. IR (ATR): 3098, 3048, 2958, 2930, 2866, 1896, 1636, 1573, 1549, 1474, 1408, 1315, 1223, 1175, 1073, 962, 839, 814, 740 cm<sup>-1</sup>. GC-MS, RT 23.29 min (*m/z* (%)): 249.9 ([M]<sup>+</sup> (100)), 214.9 (46), 188 (16), 179.0 (15), 152.0 (14), 126.0 (13), 99.0 (9), 75.0 (12), 63.0 (10), 51.0 (7). (+)ESI-HRMS (*m/z*): [M + H]<sup>+</sup> 251.01343 (error -1.18 ppm).

## General procedure for Pd-Catalyzed Amination

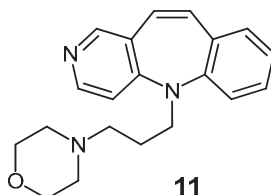


Reaction tube containing a stirring bar was evacuated and backfilled with Ar. The tube was then charged with Pd(OAc)<sub>2</sub> (5 mol %), JohnPhos (10 mol %) and NaOt-Bu (2.8 eq) and filled with Ar. Toluene was added. After stirring at room temperature for 5 min, aryl halide (1 eq) and amine (3 eq) were added, tube was filled with Ar and capped. Reaction mixture was heated to 100 °C and stirred at same temperature. Products were purified by preparative column chromatography: SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH (NH<sub>3</sub>) = 9/1.



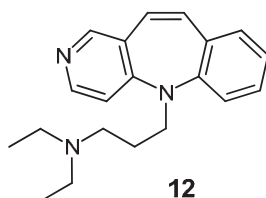
### *N,N*-Dimethyl-3-(5*H*-pyrido[4,3-*b*][1]benzazepin-5-yl)propan-1-amine (10).

Following general procedure, a mixture of **8** (24 mg, 0.080 mmol), 3-dimethylamino-1-propylamine (30  $\mu$ L, 0.24 mmol), sodium *tert*-butoxide (22 mg, 0.23 mmol), Pd(OAc)<sub>2</sub> (0.9 mg, 5 mol %), JohnPhos (2.4 mg, 10 mol %) and toluene (1.5 mL) was stirred at 100 °C for 48 hours. **10**: yellow oil (18 mg, 81%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.35 (d, *J* = 5.5 Hz, 1H), 8.17 (s, 1H), 7.30-7.22 (m, 1H), 7.05-6.98 (m, 2H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.81 (d, *J* = 5.5 Hz, 1H), 6.74 (d, *J* = 11.5 Hz, 1H), 6.60 (d, *J* = 11.5 Hz, 1H), 3.80-3.73 (m, 2H), 2.39-2.33 (m, 2H), 2.15 (s, 6H), 1.82-1.70 (m, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  158.8, 150.5, 150.1, 149.1, 134.1, 133.6, 129.5, 129.3, 129.2, 129.1, 124.1, 121.1, 114.7, 57.1, 48.2, 45.5, 25.4. IR (ATR): 3413, 3023, 2944, 2858, 2817, 2767, 1635, 1578, 1481, 1419, 1392, 1332, 1244, 1184, 1123, 1060, 919, 831, 794, 766 cm<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M + H]<sup>+</sup> 280.18125 (error: 1.51 ppm).

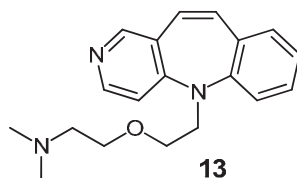


**5-[3-(Morpholin-4-yl)propyl]-5*H*-pyrido[4,3-*b*][1]benzazepine (11).** Following general procedure, a mixture of **8** (24 mg, 0.080 mmol), *N*-(3-aminopropyl)morpholine (36  $\mu$ L, 0.24 mmol), sodium *tert*-butoxide (22 mg, 0.23 mmol), Pd(OAc)<sub>2</sub> (0.9 mg, 5 mol %), JohnPhos (2.4 mg, 10 mol %) and toluene (1.5 mL) was stirred at 100 °C for 48 hours. **11**: yellow oil (16 mg, 61%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.35 (d, *J* = 6.0 Hz, 1H), 8.17 (s, 1H), 7.29-7.24 (m, 1H), 7.05-7.00 (m, 2H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.80 (d, *J* = 5.5 Hz, 1H), 6.73 (d, *J* = 11.5 Hz, 1H), 6.59 (d, *J* = 11.5 Hz, 1H), 3.80-3.75 (m, 2H), 3.70-3.60 (m, 4H), 2.47-2.40 (m, 2H), 2.39-2.30 (m, 4H), 1.80-1.70 (m, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  158.8, 150.5, 150.1, 149.0, 134.1, 133.6, 129.5, 129.3, 129.2, 124.1, 121.1, 114.7, 66.9, 56.2, 53.7, 48.2, 24.2. IR (ATR): 3268, 3025, 2956, 2854, 2812, 2687, 1640, 1576, 1523, 1479, 1395, 1332, 1307, 1184, 1141, 1118, 1068, 914, 765, 735, 700 cm<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M + H]<sup>+</sup> 322.19242 (error: 3.20 ppm).

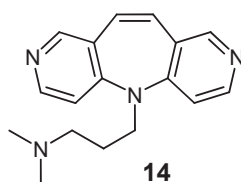




***N,N*-Diethyl-3-(5*H*-pyrido[4,3-*b*][1]benzazepin-5-yl)propan-1-amine (12).** Following general procedure, a mixture of **8** (24 mg, 0.080 mmol), 3-diethylamino-1-propylamine (38  $\mu$ L, 0.24 mmol), sodium *tert*-butoxide (22 mg, 0.23 mmol), Pd(OAc)<sub>2</sub> (0.9 mg, 5 mol %), JohnPhos (2.4 mg, 10 mol %) and toluene (1.5 mL) was stirred at 100 °C for 48 hours. **12**: yellow oil (20 mg, 79%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.36 (d, *J* = 5.5 Hz, 1H), 8.18 (s, 1H), 7.29-7.24 (m, 1H), 7.05-6.98 (m, 2H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 6.0 Hz, 1H), 6.74 (d, *J* = 11.5 Hz, 1H), 6.60 (d, *J* = 11.0 Hz, 1H), 3.80-3.73 (m, 2H), 2.62-2.55 (m, 2H), 2.51-2.42 (m, 4H), 1.79-1.70 (m, 2H), 0.98-0.80 (m, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  158.8, 150.4, 150.1, 149.0, 134.1, 133.6, 129.5, 129.3, 129.2, 129.1, 124.1, 121.2, 114.7, 49.6, 48.1, 46.8, 24.2, 11.3. IR (ATR): 3371, 3200, 2974, 1675, 1581, 1478, 1395, 1342, 1244, 1184, 1128, 794, 766, 651 cm<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M + 2H]<sup>2+</sup> 154.60980 (error: 0.62 ppm), [M + H]<sup>+</sup> 308.21276 (error: 2.05 ppm).



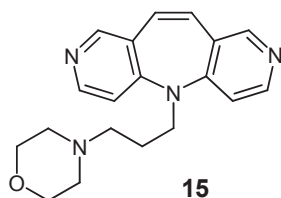
***N,N*-Dimethyl-2-[2-(5*H*-pyrido[4,3-*b*][1]benzazepin-5-yl)ethoxy]ethanamine (13).** Following general procedure, a mixture of **8** (24 mg, 0.080 mmol), 2-(2-dimethylamino-ethoxy)-ethylamine (35  $\mu$ L, 0.24 mmol), sodium *tert*-butoxide (22 mg, 0.23 mmol), Pd(OAc)<sub>2</sub> (0.9 mg, 5 mol %), JohnPhos (2.4 mg, 10 mol %) and toluene (1.5 mL) was stirred at 100 °C for 48 hours. **13**: yellow oil (15 mg, 61%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.36 (d, *J* = 6.0 Hz, 1H), 8.18 (s, 1H), 7.30-7.25 (m, 1H), 7.06-7.01 (m, 2H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 5.5 Hz, 1H), 6.74 (d, *J* = 11.5 Hz, 1H), 6.60 (d, *J* = 11.5 Hz, 1H), 4.00-3.93 (m, 2H), 3.64-3.59 (m, 2H), 3.54-3.49 (m, 2H), 2.50-2.45 (m, 2H), 2.25 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  158.6, 150.5, 150.1, 148.9, 134.2, 133.5, 129.6, 129.4, 129.1, 129.0, 124.3, 121.0, 114.6, 69.0, 68.2, 58.6, 50.0, 45.5. IR (ATR): 3397, 3025, 2943, 2867, 2821, 2774, 1673, 1578, 1482, 1461, 1395, 1329, 1249, 1186, 1126, 1061, 916, 835, 769 cm<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M + H]<sup>+</sup> 310.19001 (error: -4.46 ppm).



**3-(5*H*-Dipyrido[4,3-*b*:3',4'-*f*]azepin-5-yl)-*N,N*-dimethylpropan-1-amine (14).**

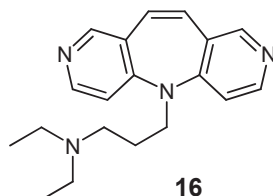
Following general procedure, a mixture of **9** (150 mg, 0.597 mmol), 3-dimethylamino-1-propylamine (225  $\mu$ L, 1.80 mmol), sodium *tert*-butoxide (161 mg, 1.68 mmol), Pd(OAc)<sub>2</sub> (6.7 mg, 5 mol %), JohnPhos (18 mg, 10 mol %) and toluene (7.5 mL) was stirred at 100 °C for 24 hours. **14**: yellow oil 146 mg (87%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.39 (d, *J* = 5.5 Hz, 2H), 8.16 (s, 2H), 6.77 (d, *J* = 5.5 Hz, 2H), 6.64 (s, 2H), 3.78-3.69 (m, 2H), 2.39-2.33 (m, 2H), 2.16 (s, 6H), 1.81-1.72 (m, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  157.1, 150.7, 150.7, 131.1, 128.6, 115.4, 56.7, 47.8, 45.5, 25.0. IR (film): 3382, 2948, 2864, 2823, 2780, 1641, 1579, 1479, 1398, 1335, 1248, 1176, 1062, 972, 932, 840 cm<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M+2H]<sup>2+</sup>, 141.09229 (error 4.33), [M+H]<sup>+</sup> 281.17638 (error 1.10).





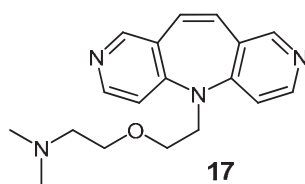
**15**

**5-[3-(Morpholin-4-yl)propyl]-5H-dipyrido[4,3-*b*:3',4'-*f*]azepine (15).** Following general procedure, a mixture of **9** (40 mg, 0.16 mmol), *N*-(3-aminopropyl)morpholine (70  $\mu$ L, 0.48 mmol), sodium *tert*-butoxide (43 mg, 0.45 mmol), Pd(OAc)<sub>2</sub> (1.8 mg, 5 mol %), JohnPhos (4.8 mg, 10 mol %) and toluene (2.5 mL) was stirred at 100 °C for 24 hours. **15**: yellow oil (36 mg, 69%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.39 (d, *J* = 5.5 Hz, 2H), 8.16 (s, 2H), 6.76 (d, *J* = 5.5 Hz, 2H), 6.63 (s, 2H), 3.81-3.76 (m, 2H), 3.66–3.57 (m, 4H), 2.48-2.41 (m, 2H), 2.40-2.34 (m, 4H) 1.82-1.74 (m, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  157.1, 150.8, 131.2, 128.7, 115.4, 66.9, 55.8, 53.8, 47.8, 24.0. IR (ATR): 3627, 3386, 3028, 2954, 2854, 2812, 2687, 1672, 1638, 1576, 1480, 1397, 1334, 1252, 1178, 1140, 1117, 1064, 920, 843, 780, 735 cm<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M+2H]<sup>2+</sup>, 162.09687 (error -0.55), [M+H]<sup>+</sup> 323.18606 (error: -1.79 ppm).



**16**

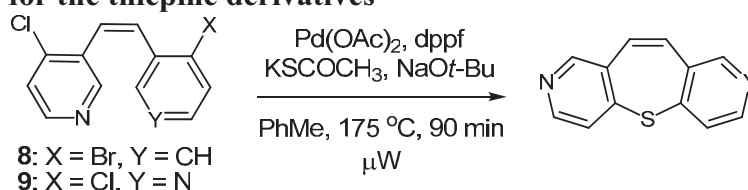
**3-(5H-Dipyrido[4,3-*b*:3',4'-*f*]azepin-5-yl)-*N,N*-diethylpropan-1-amine (16).** Following general procedure, a mixture of **9** (20 mg, 0.080 mmol), 3-diethylamino-1-propylamine (38  $\mu$ L, 0.24 mmol), sodium *tert*-butoxide (22 mg, 0.23 mmol), Pd(OAc)<sub>2</sub> (0.9 mg, 5 mol %), JohnPhos (2.4 mg, 10 mol %) and toluene (1.5 mL) was stirred at 100 °C for 24 hours. **16**: yellow oil (12 mg, 47%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.39 (d, *J* = 5.5 Hz, 2H), 8.16 (s, 2H), 6.76 (d, *J* = 5.5 Hz, 2H), 6.64 (s, 2H), 3.80-3.74 (m, 2H), 2.56-2.49 (m, 2H), 2.48-2.39 (m, 4H), 1.78-1.64 (m, 2H), 0.98-0.90 (m, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  157.2, 150.8, 150.8, 131.2, 128.7, 115.5, 49.6, 47.8, 47.1, 24.6, 11.7. IR (ATR): 3354, 3166, 2821, 1652, 1470, 1398, 1154, 1050, 1007, 878, 830 cm<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M+H]<sup>+</sup> 309.20590 (error: -4.78 ppm).



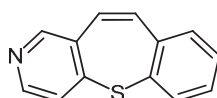
**17**

**2-[2-(5H-Dipyrido[4,3-*b*:3',4'-*f*]azepin-5-yl)ethoxy]-*N,N*-dimethylethanamine (17).** Following general procedure, a mixture of **9** (20 mg, 0.080 mmol), 2-(2-dimethylamino-ethoxy)-ethylamine (35  $\mu$ L, 0.24 mmol), sodium *tert*-butoxide (22 mg, 0.23 mmol), Pd(OAc)<sub>2</sub> (0.9 mg, 5 mol %), JohnPhos (2.4 mg, 10 mol %) and toluene (1.5 mL) was stirred at 100 °C for 24 hours. **17**: yellow oil (13 mg, 54%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.40 (d, *J* = 5.5 Hz, 2H), 8.17 (s, 2H), 6.78 (d, *J* = 5.5 Hz, 2H), 6.64 (s, 2H), 3.99-3.94 (m, 2H), 3.68-3.62 (m, 2H), 3.53-3.47 (m, 2H), 2.46-2.41 (m, 2H), 2.22 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  156.9, 150.9, 150.8, 131.2, 128.6, 115.3, 69.4, 67.8, 58.8, 49.6, 45.8. IR (ATR): 3408, 2947, 2873, 2825, 2781, 1665, 1581, 1485, 1400, 1333, 1254, 1176, 1127, 1064, 929, 844, 800, 738 cm<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M+2H]<sup>2+</sup>, 156.09666 (error -1.90), [M+H]<sup>+</sup> 311.18522 (error: -4.55 ppm).

### General procedure for the thiepine derivatives

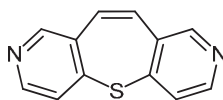


Reaction tube containing a stirring bar was evacuated and backfilled with Ar. The tube was charged with Pd(OAc)<sub>2</sub> (5 mol %), dppf (10 mol %), NaOt-Bu (1.2 eq), aryl halide (1 eq) and KSCoCH<sub>3</sub> (1.2 eq) and evacuated and backfilled with Ar. The flask was capped with a rubber septum, and toluene was added. The reaction mixture was heated in a Biotage Initiator 2.5 microwave at 175 °C for 90 min. After completion, the reaction mixture was cooled to room temperature. Products were purified by preparative column chromatography: SiO<sub>2</sub>, Hexane/EtOAc = 1/1.



**18**

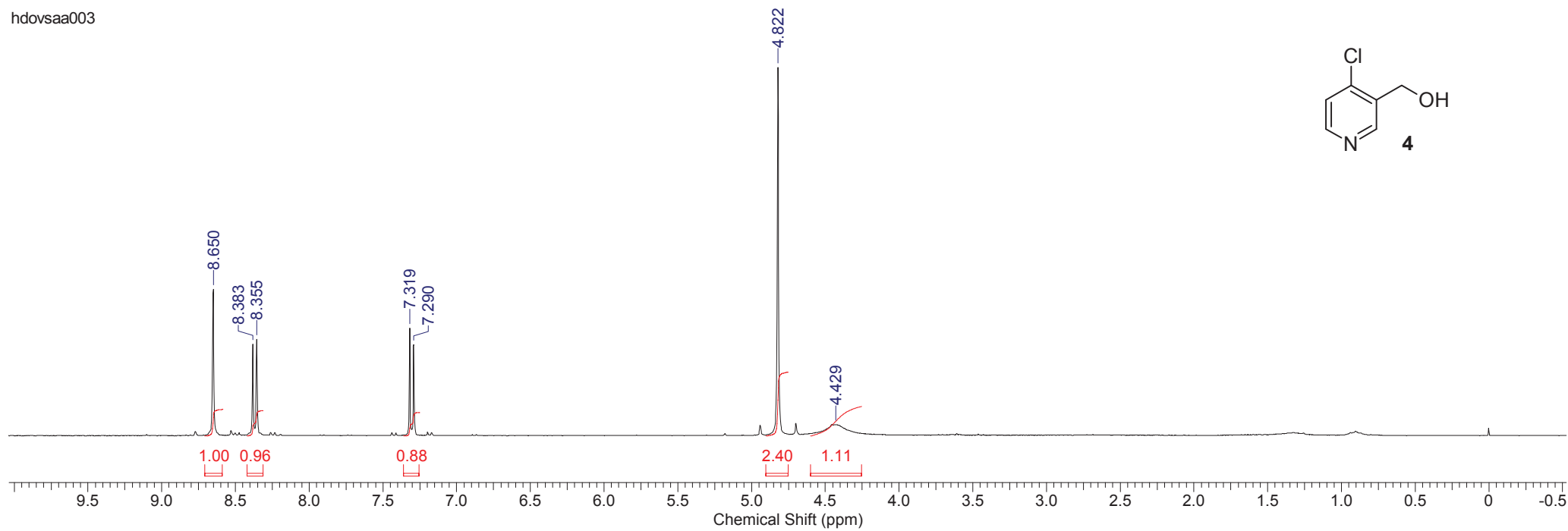
**[1]Benzothiepine[3,2-*c*]pyridine (18).** Following general procedure, a mixture of **8** (35 mg, 0.12 mmol), KSCoCH<sub>3</sub> (16 mg, 0.14 mmol), sodium *tert*-butoxide (14 mg, 0.14 mmol), Pd(OAc)<sub>2</sub> (1.3 mg, 5 mol %), dppf (6.6 mg, 10 mol %) and toluene (1.5 mL) was heated in a Biotage Initiator 2.5 microwave at 175 °C for 90 min. **18**: white solid (13 mg, 51%), mp 80-82 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.48-8.44 (m, 2H), 7.48-7.44 (m, 1H), 7.36-7.28 (m, 3H), 7.28-7.24 (m, 1H), 7.13 (d, *J* = 12.5 Hz, 1H), 6.99 (d, *J* = 12.5 Hz, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 149.9, 149.8, 144.7, 139.7, 136.1, 135.4, 133.0, 132.7, 130.4, 129.9, 129.7, 128.7, 126.3. IR (ATR): 3056, 3025, 2927, 2855, 1738, 1629, 1563, 1538, 1471, 1442, 1416, 1389, 1306, 1275, 1174, 1056, 885, 836 cm<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M + H]<sup>+</sup> 212.05209 (error -3.58 ppm).



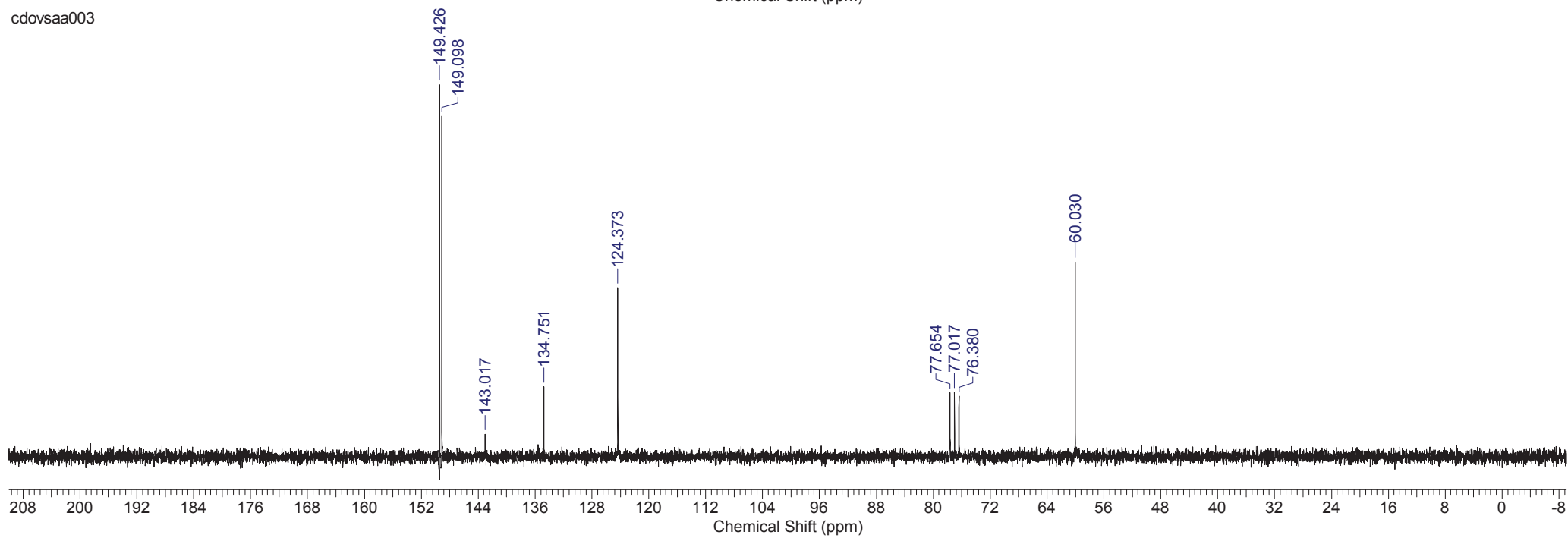
**19**

**Thiepine[3,2-*c*:6,7-*c'*]dipyridine (19).** Following general procedure, a mixture of **9** (30 mg, 0.12 mmol), KSCoCH<sub>3</sub> (16 mg, 0.14 mmol), sodium *tert*-butoxide (14 mg, 0.14 mmol), Pd(OAc)<sub>2</sub> (1.3 mg, 5 mol %), dppf (7 mg, 10 mol %) and toluene (1.5 mL) was heated in a Biotage Initiator 2.5 microwave at 175 °C for 90 min. **19**: white solid (12 mg, 49%), mp 139-140 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 8.51 (d, *J* = 5.0 Hz, 2H), 8.47 (s, 2H), 7.32 (d, *J* = 5.0 Hz, 2H), 7.08 (s, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 150.6, 150.3, 142.9, 134.9, 132.8, 126.6. IR (film): 3024, 2930, 1565, 1542, 1473, 1390, 1294, 1268, 1178, 1047, 885, 835 cm<sup>-1</sup>. (+)ESI-HRMS (*m/z*): [M + H]<sup>+</sup> 213.04721 (error -4.14 ppm).

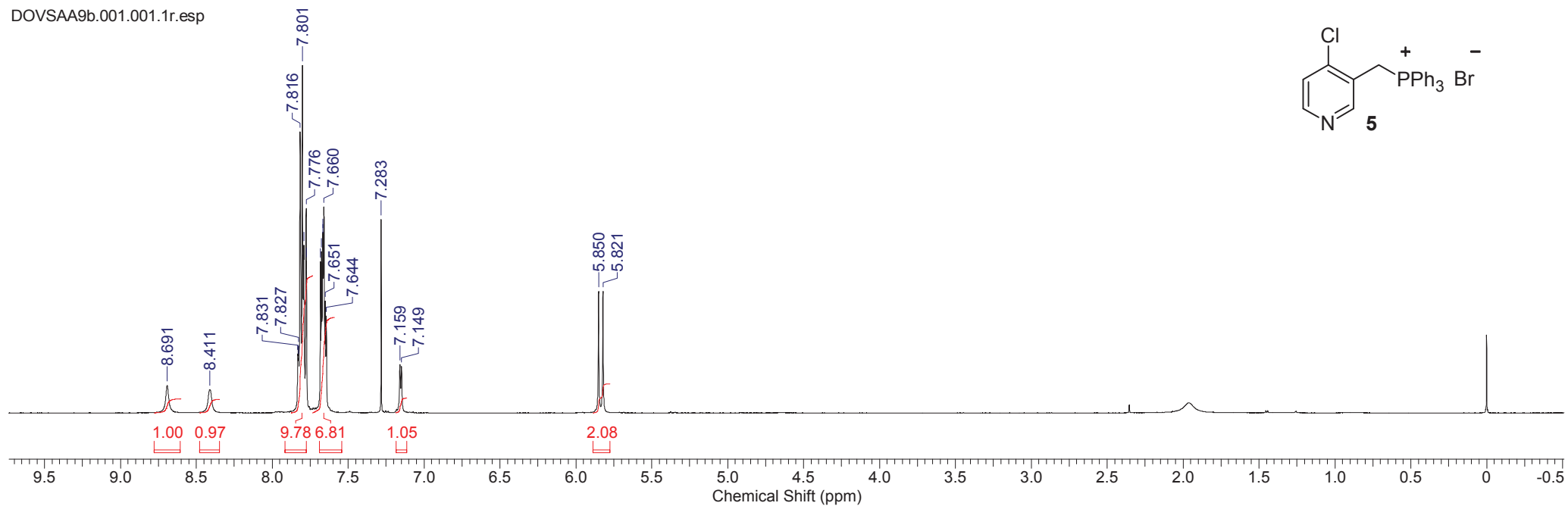
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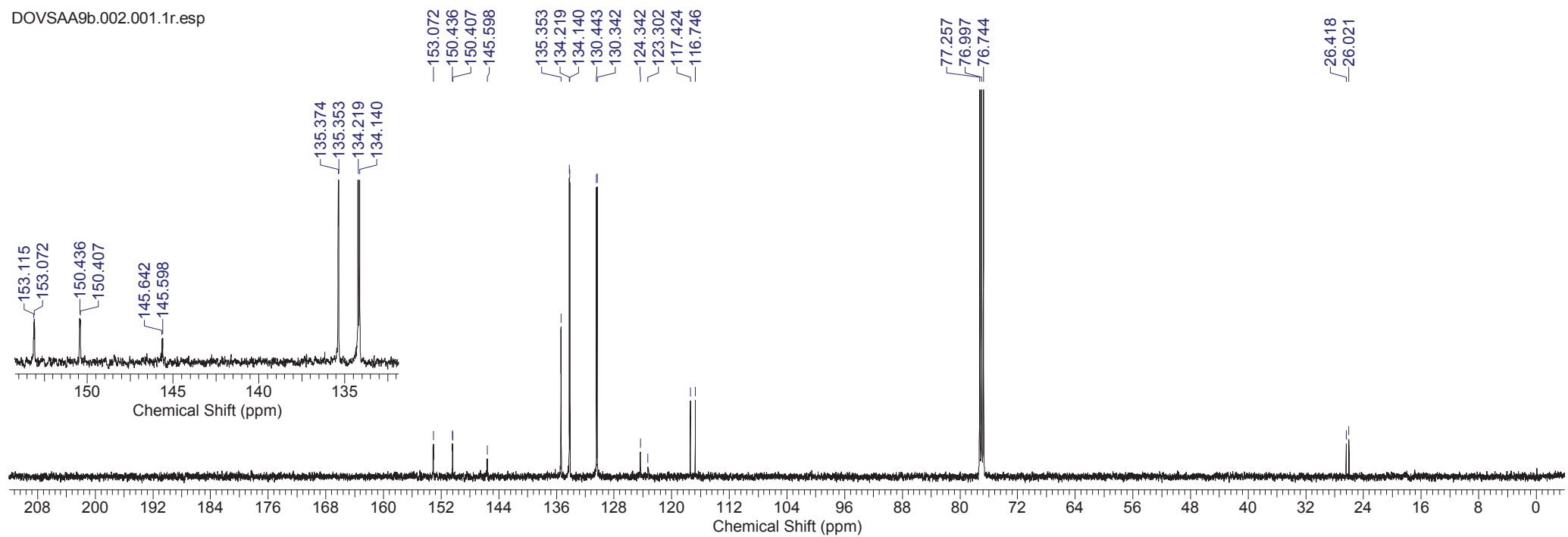
cdovsaa003



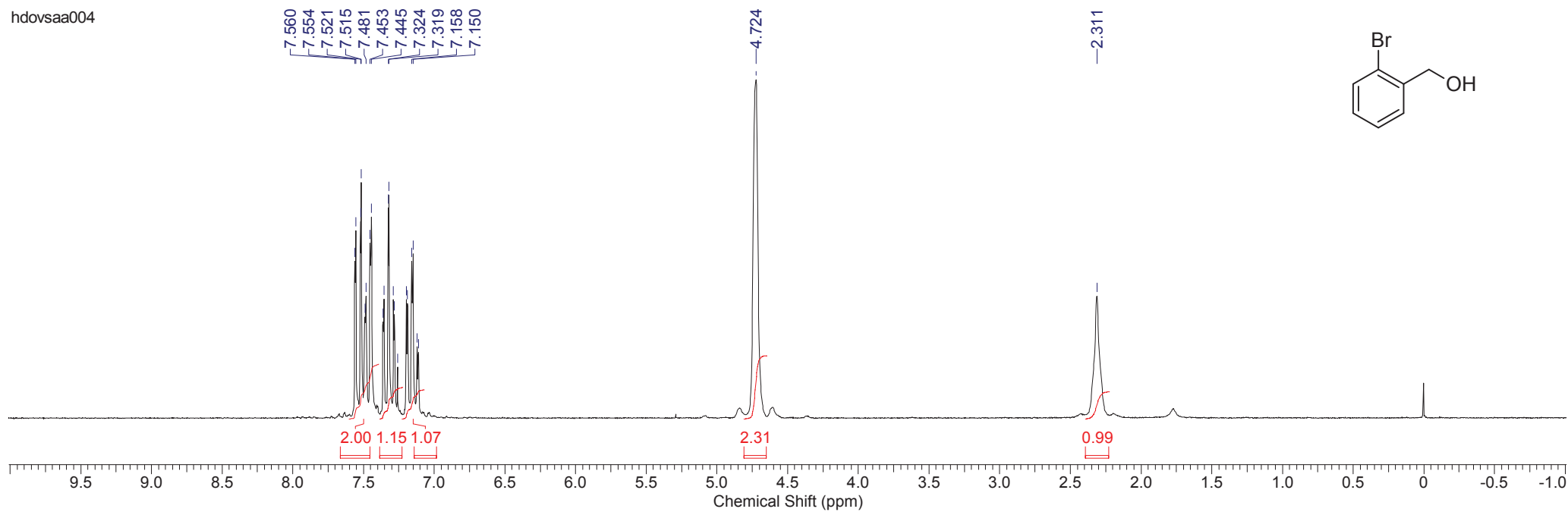
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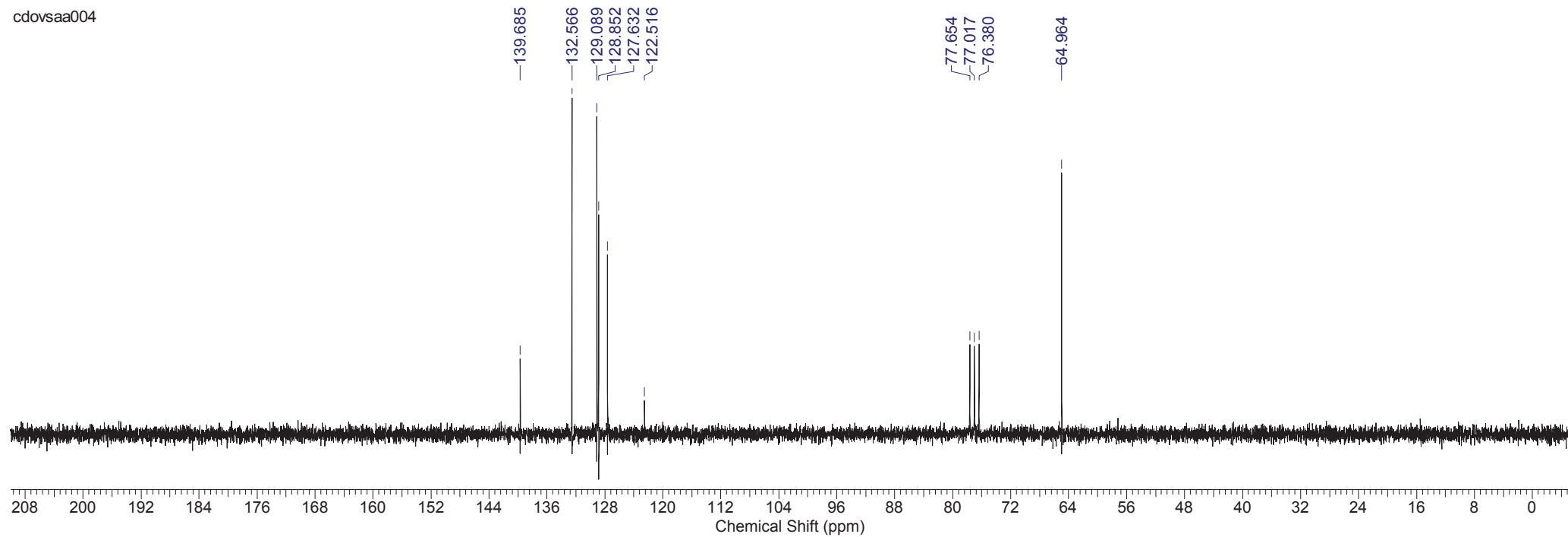
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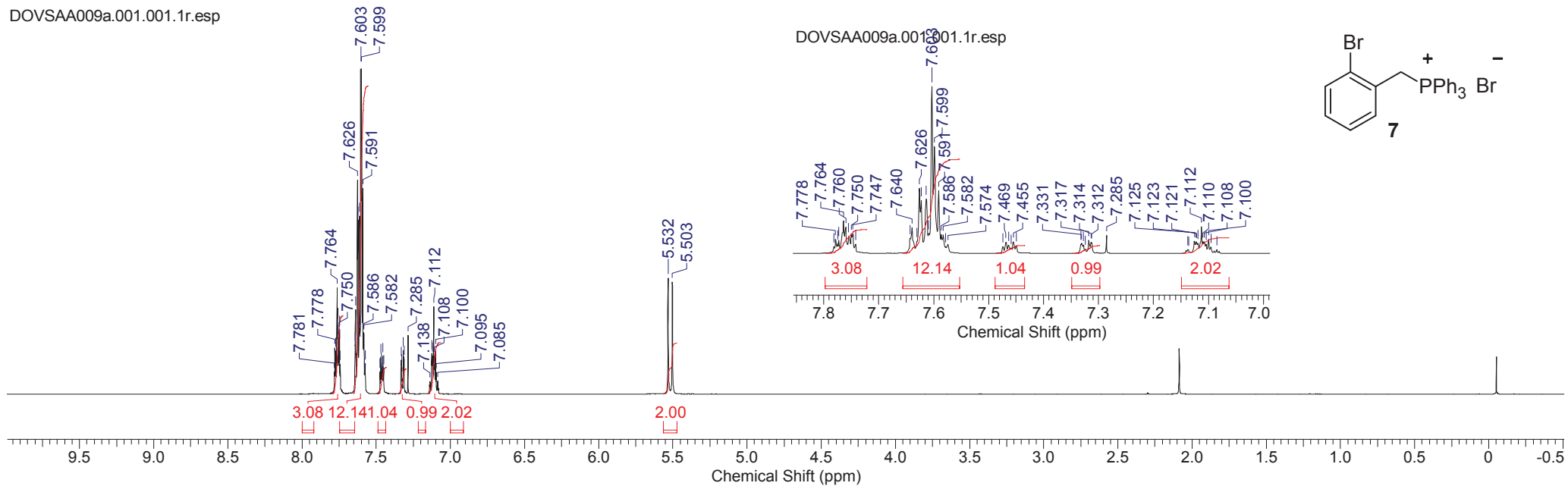
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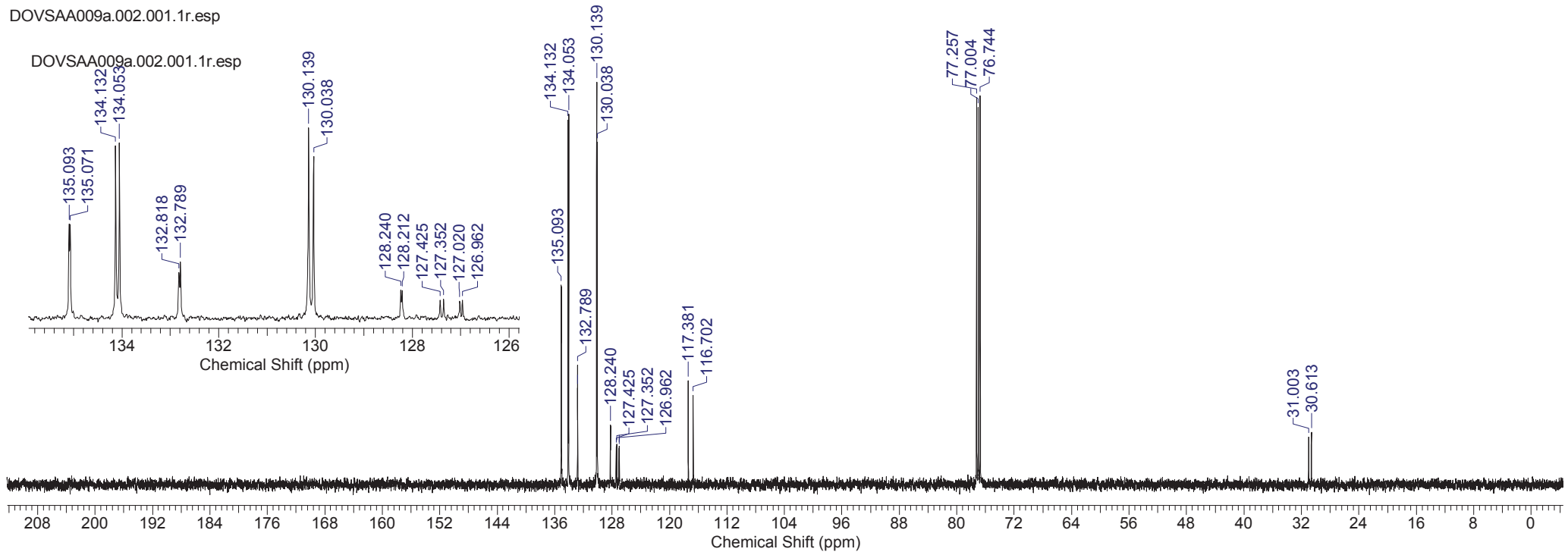
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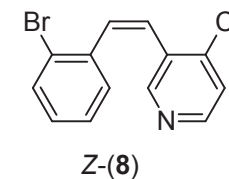
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**Chemical Structure of 8:** BrC1=CC=CC=C1/C=C/C2=CC=CC=N2Cl

**<sup>1</sup>H NMR Spectrum (CDCl<sub>3</sub>):**

Chemical Shift (ppm)	Integration
8.299, 8.161	1.00, 0.96
7.593, 7.578	1.01
7.318, 7.308, 7.263, 7.081, 7.097	1.04, 2.06
6.946, 6.922, 6.762, 6.738	1.99, 1.01
8.299, 8.288, 8.161	1.00, 0.96
7.596, 7.593, 7.581, 7.578	1.01
7.318, 7.308, 7.263	1.04
7.100, 7.085, 7.081, 7.097, 7.070, 7.059, 7.044	2.06
6.950, 6.946, 6.922	1.99
6.762, 6.738	1.01



NB26cis.002.001.1r.esp



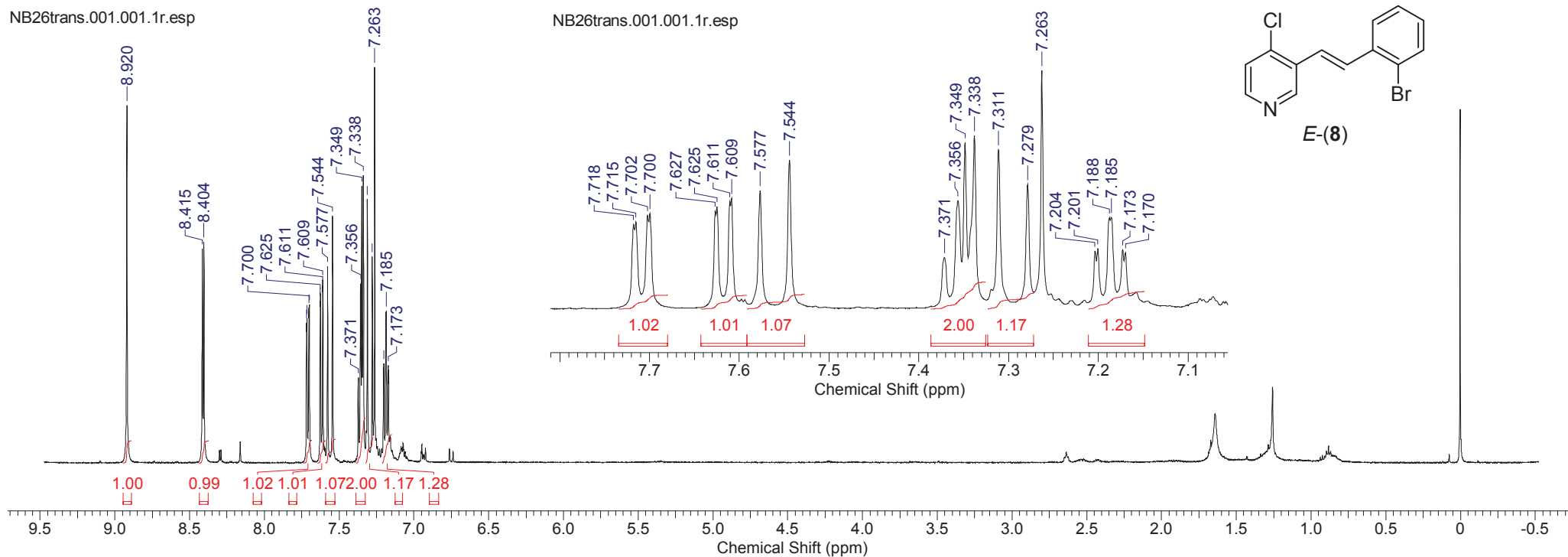
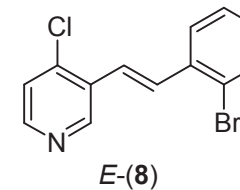
The <sup>13</sup>C NMR spectrum shows a series of peaks in the aromatic and carbonyl region (123-152 ppm) and a triplet for the CDCl<sub>3</sub> solvent at 77 ppm. The x-axis is labeled 'Chemical Shift (ppm)' and ranges from 0 to 208.

Chemical Shift (ppm)
151.170
148.700
143.162
136.447
133.400
132.880
131.501
130.404
129.256
127.212
124.844
124.245
123.905
77.204
76.951
76.698



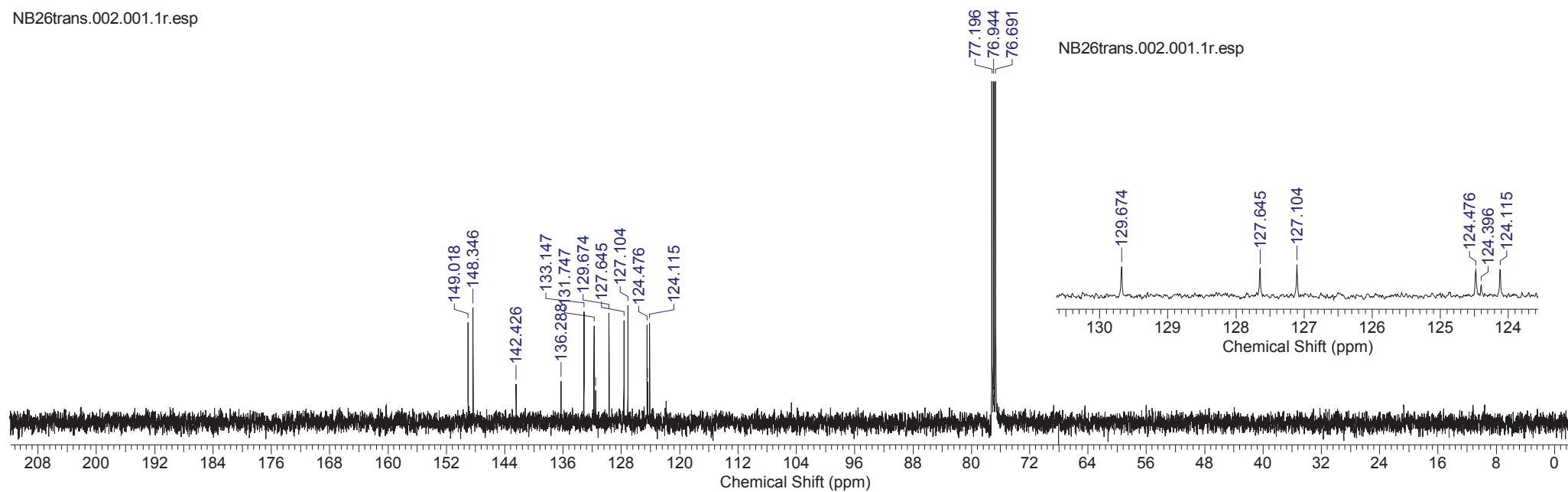
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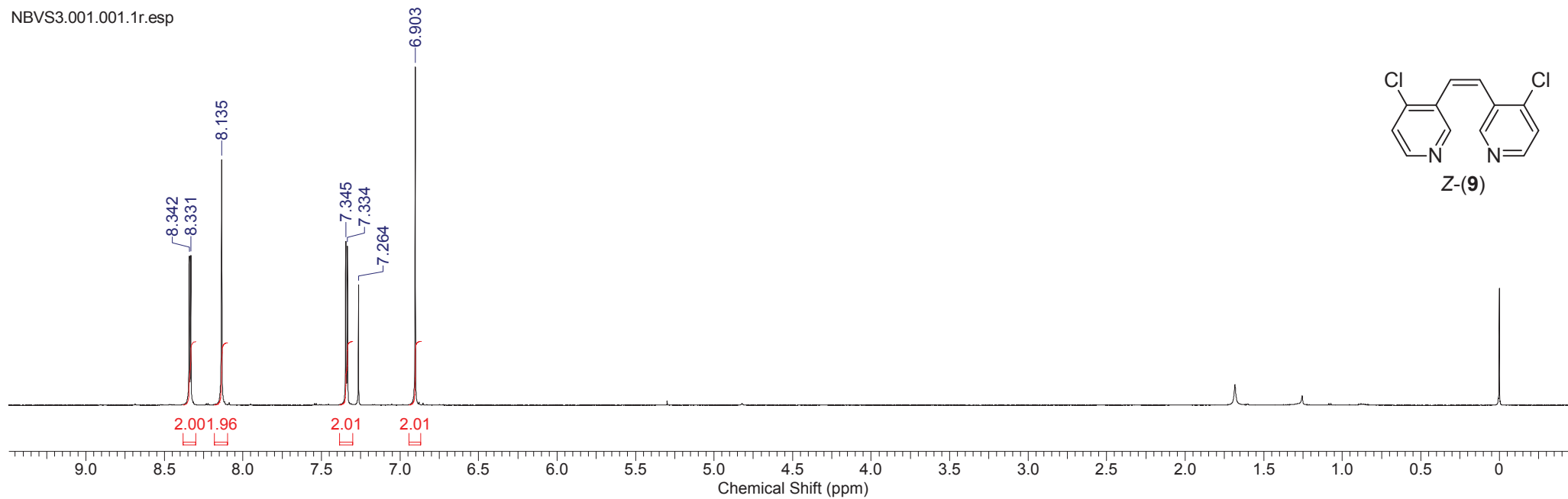


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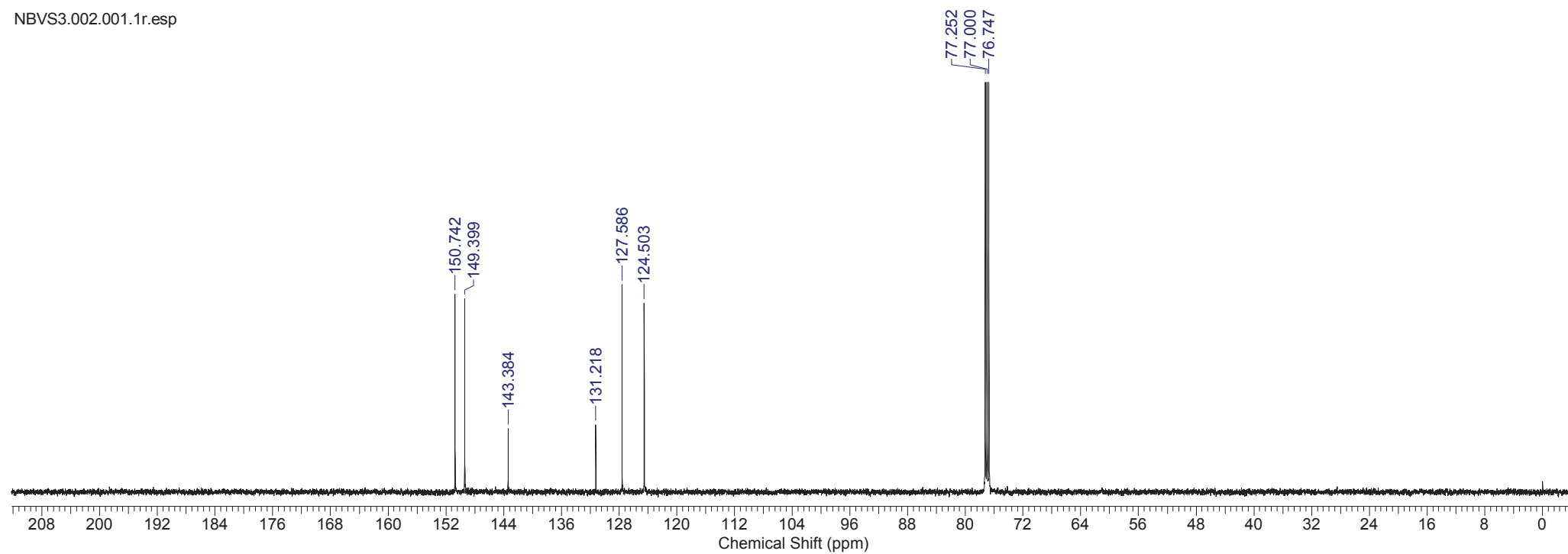
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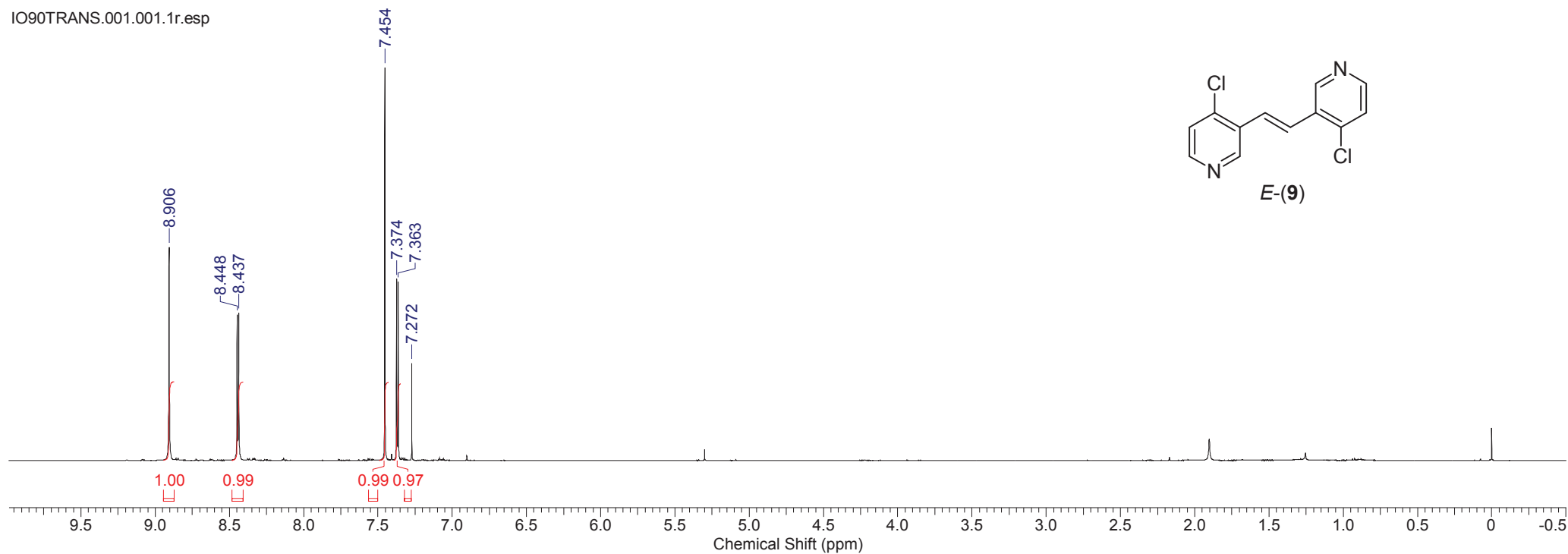
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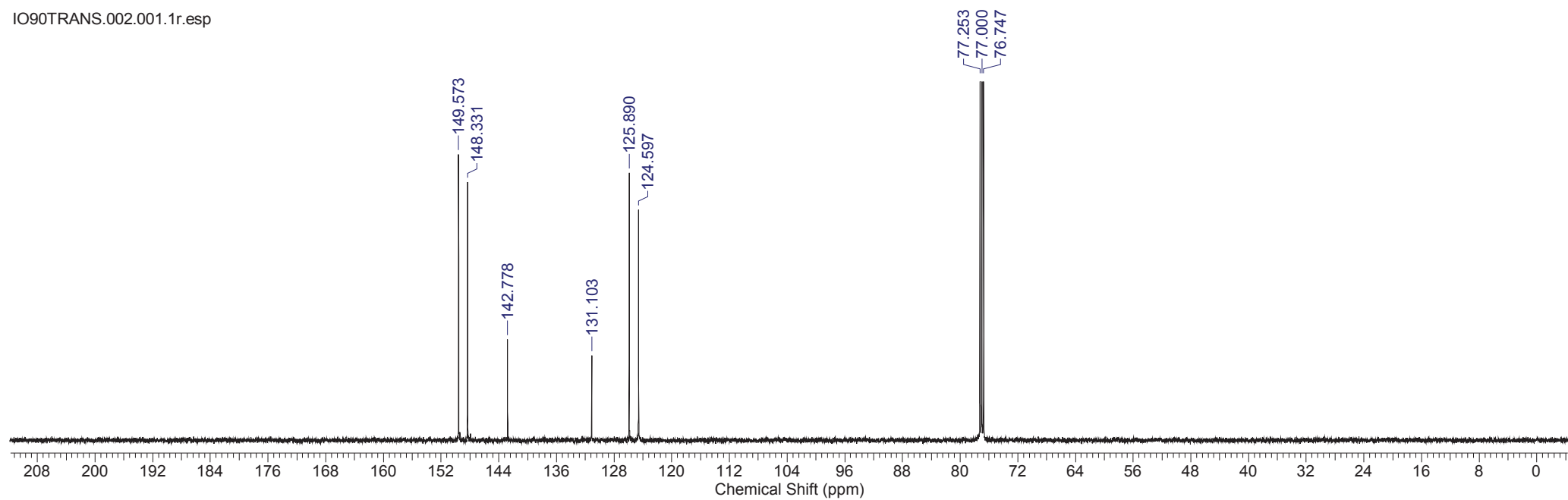
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IO90TRANS.001.001.1r.esp

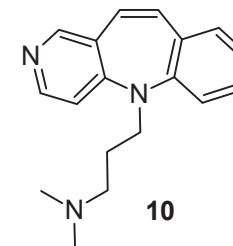
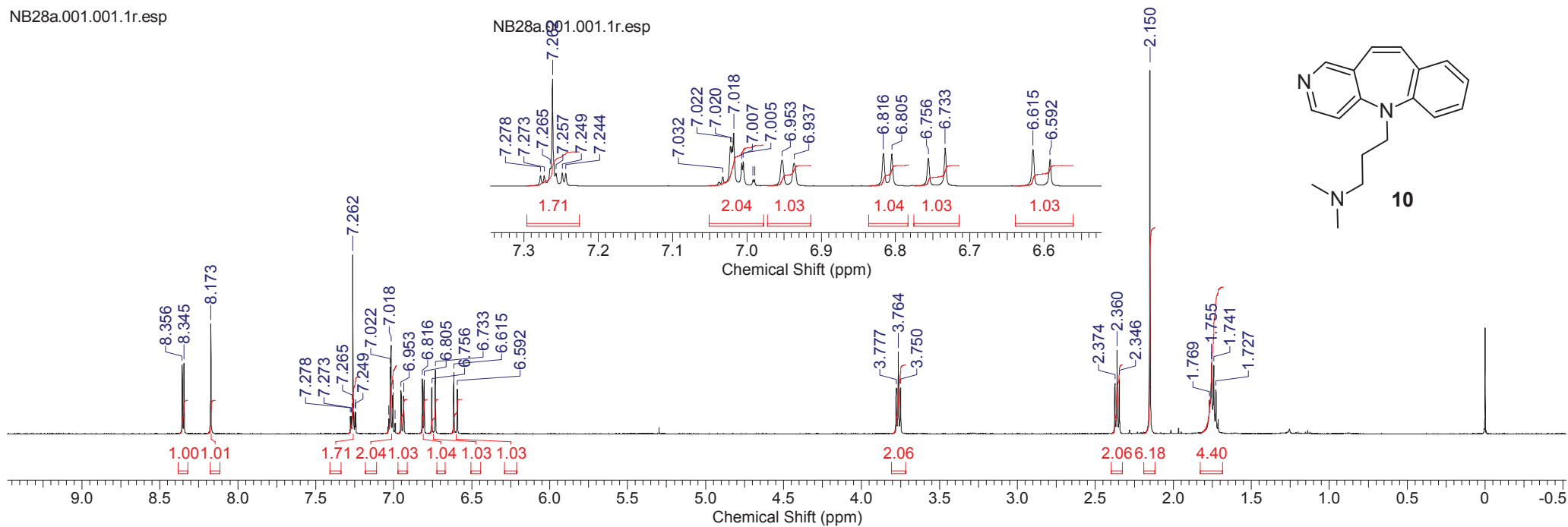


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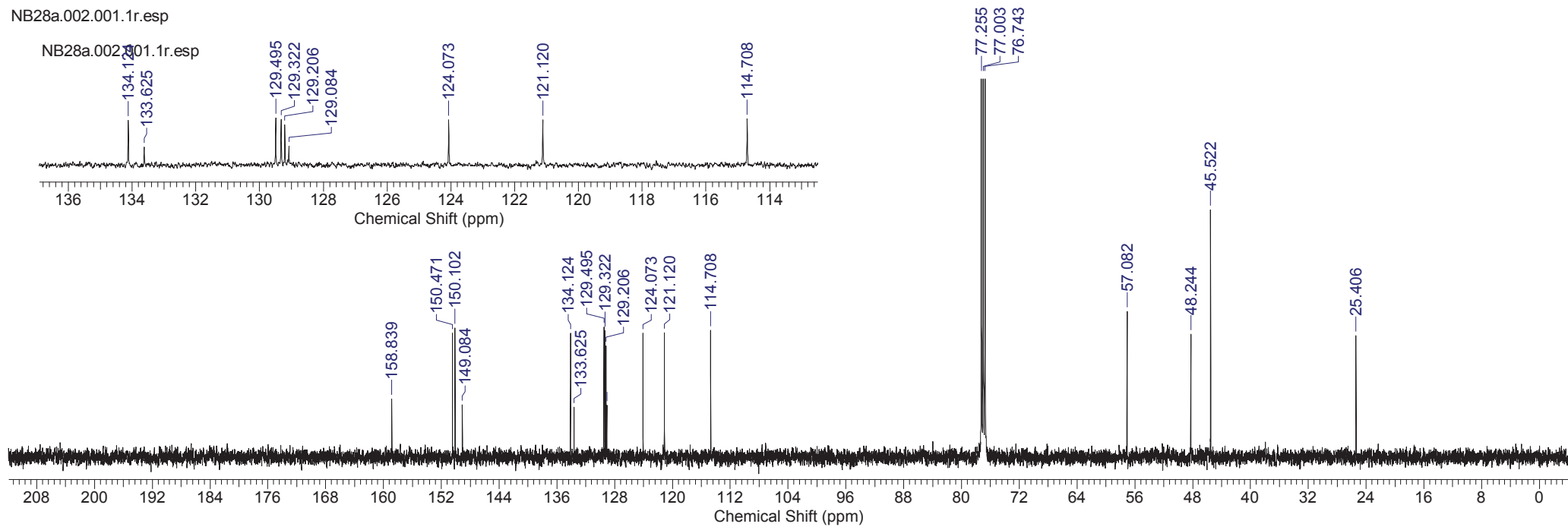
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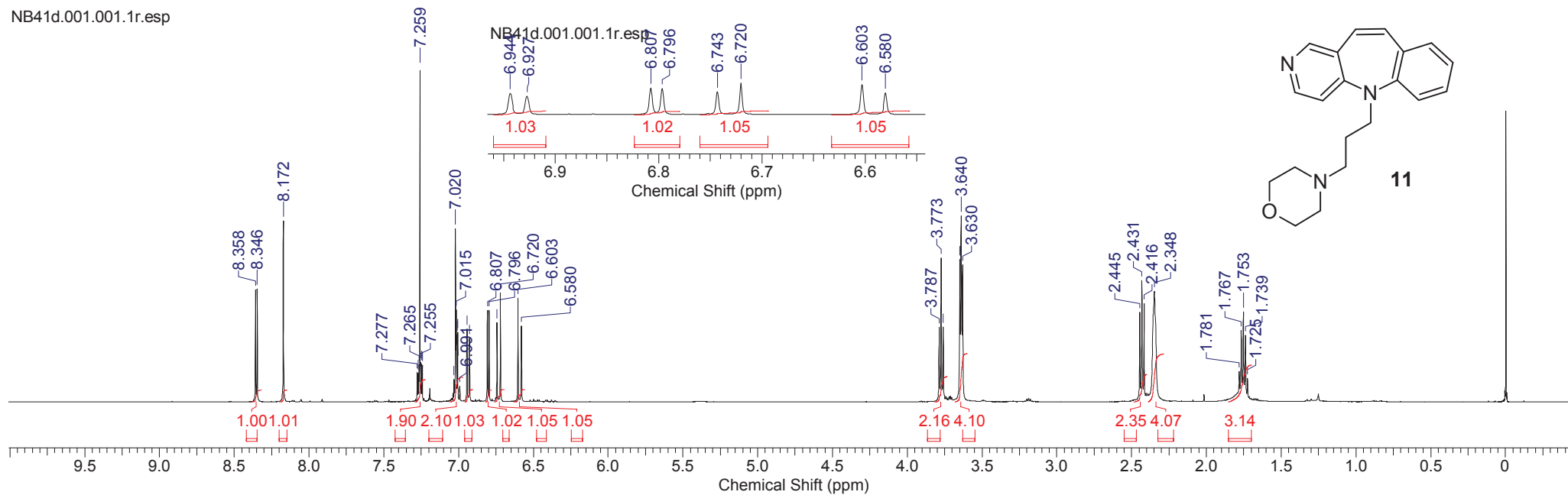


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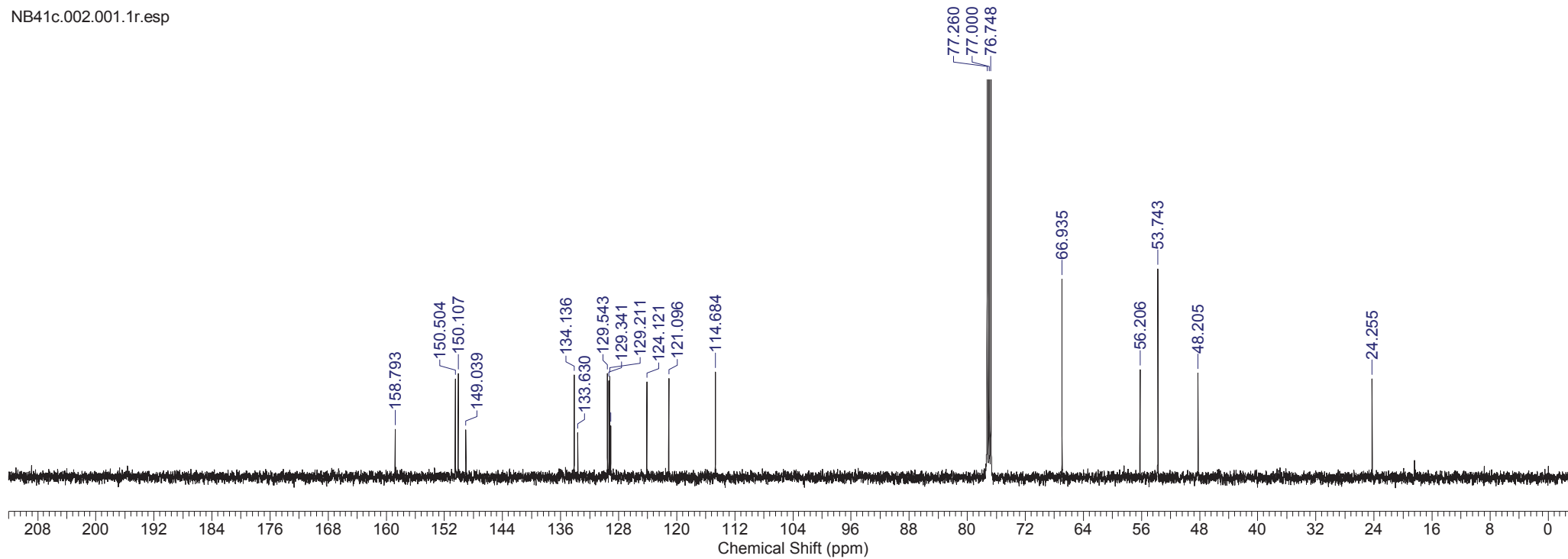
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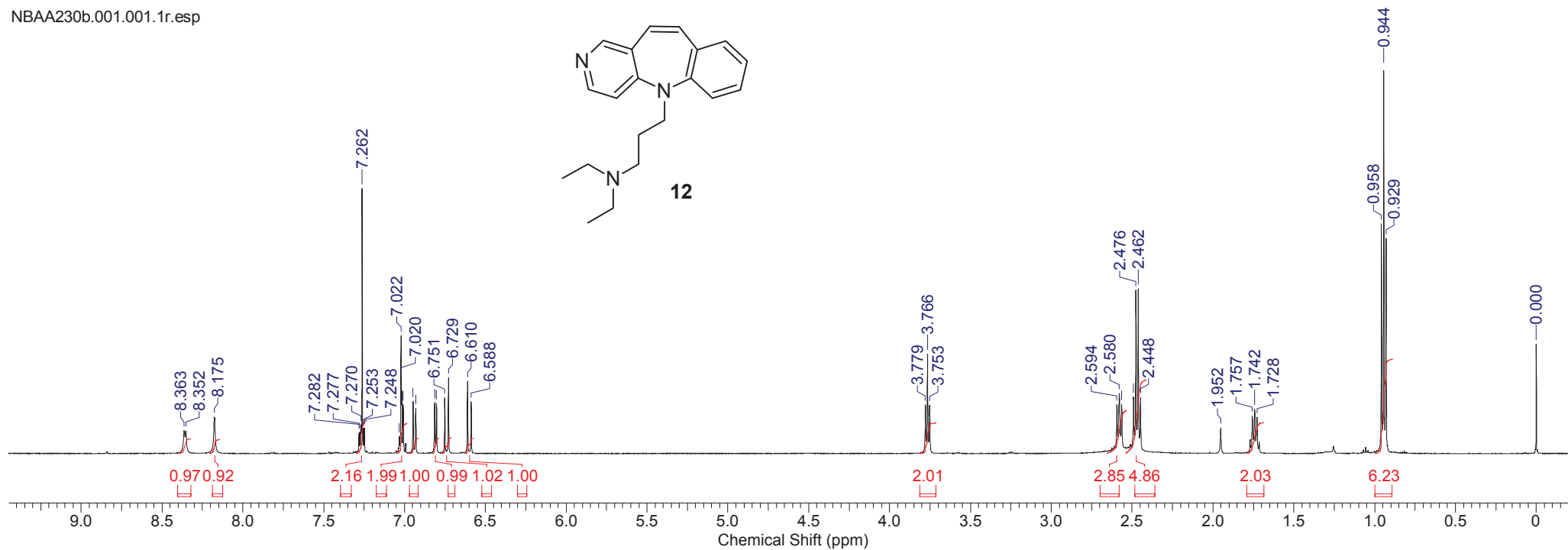
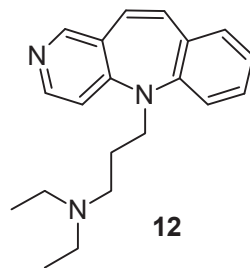
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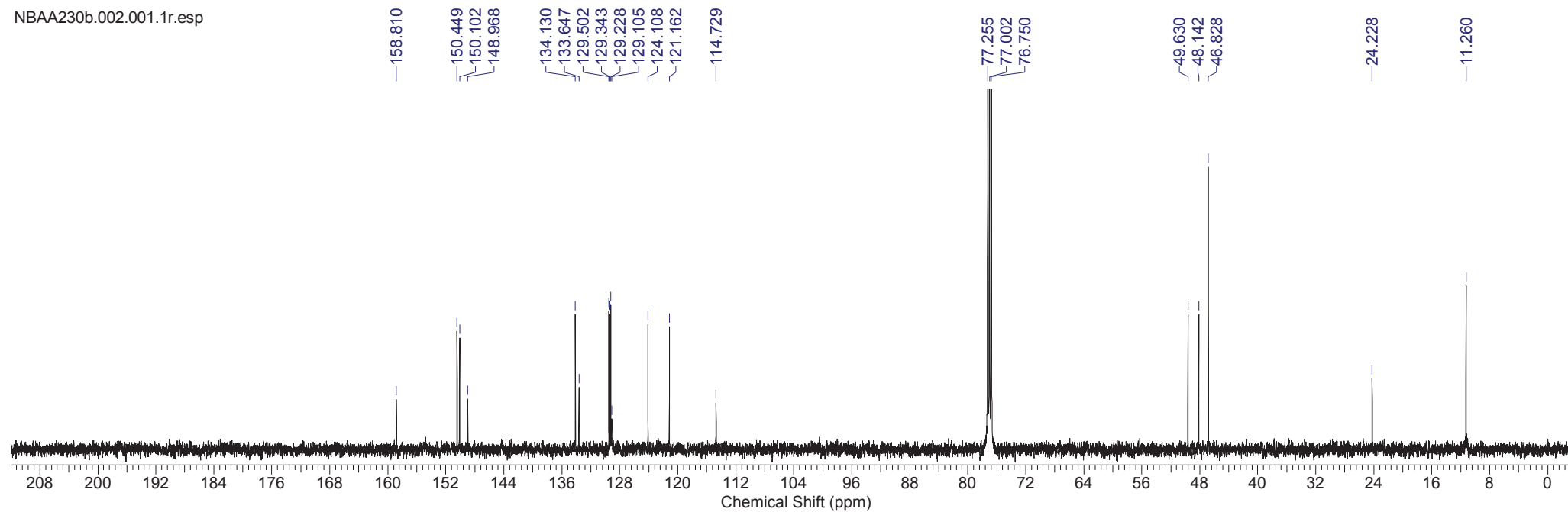
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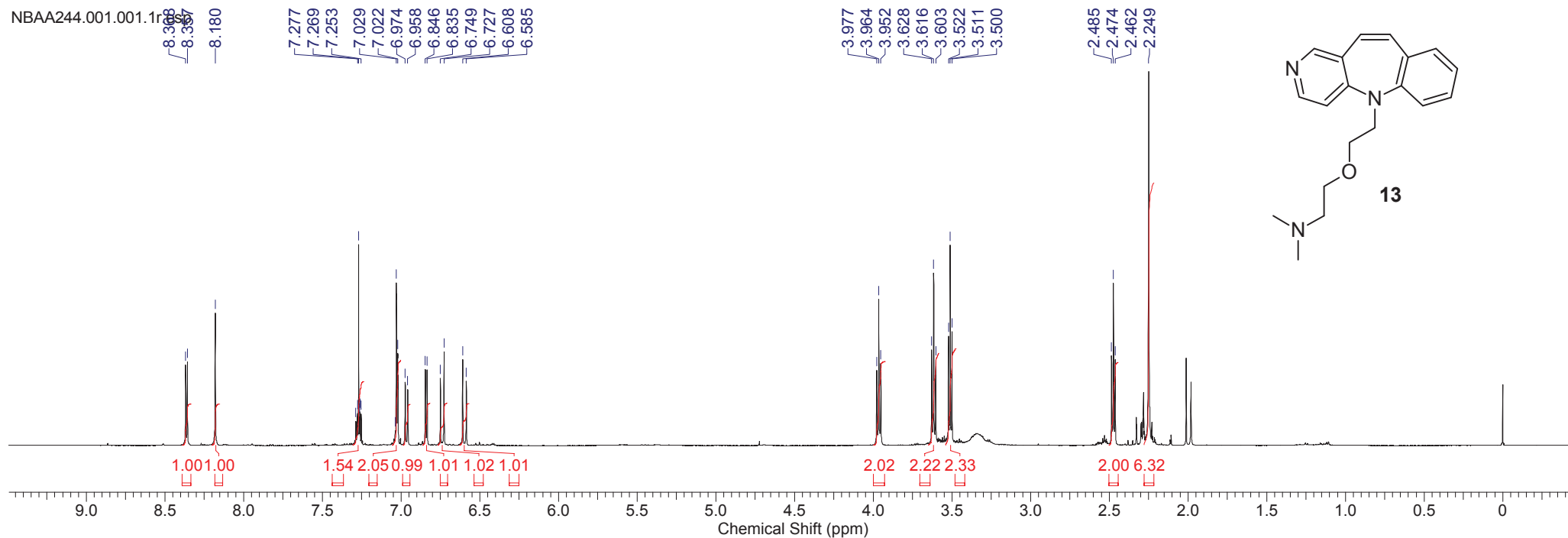
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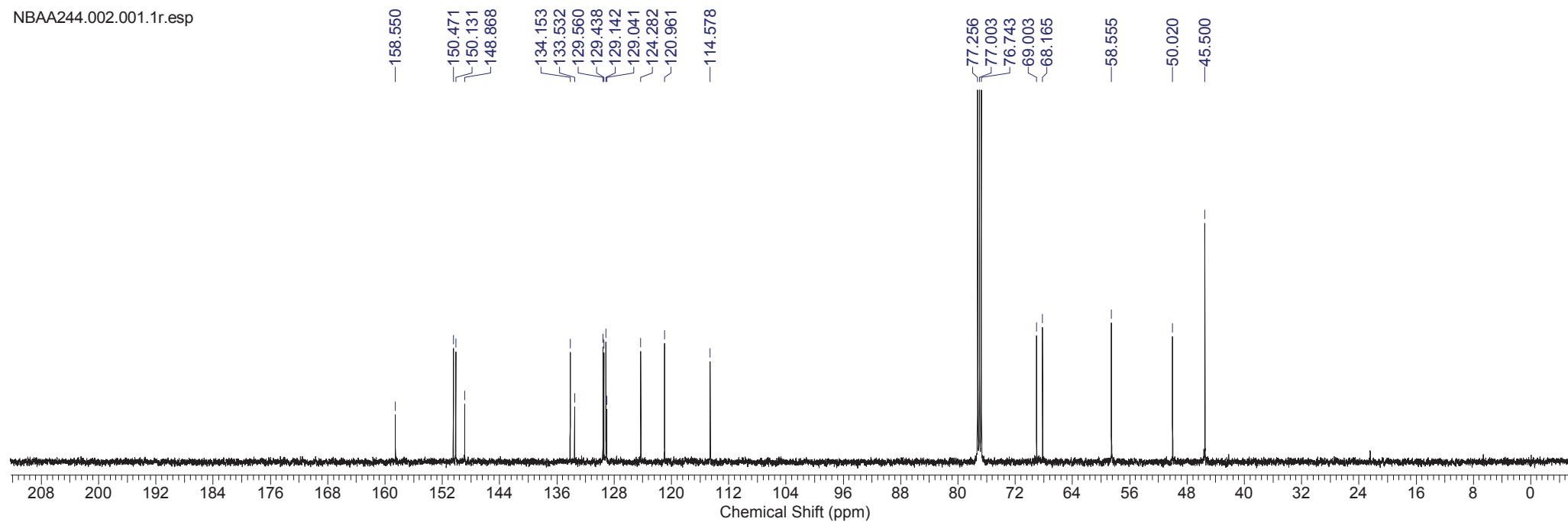
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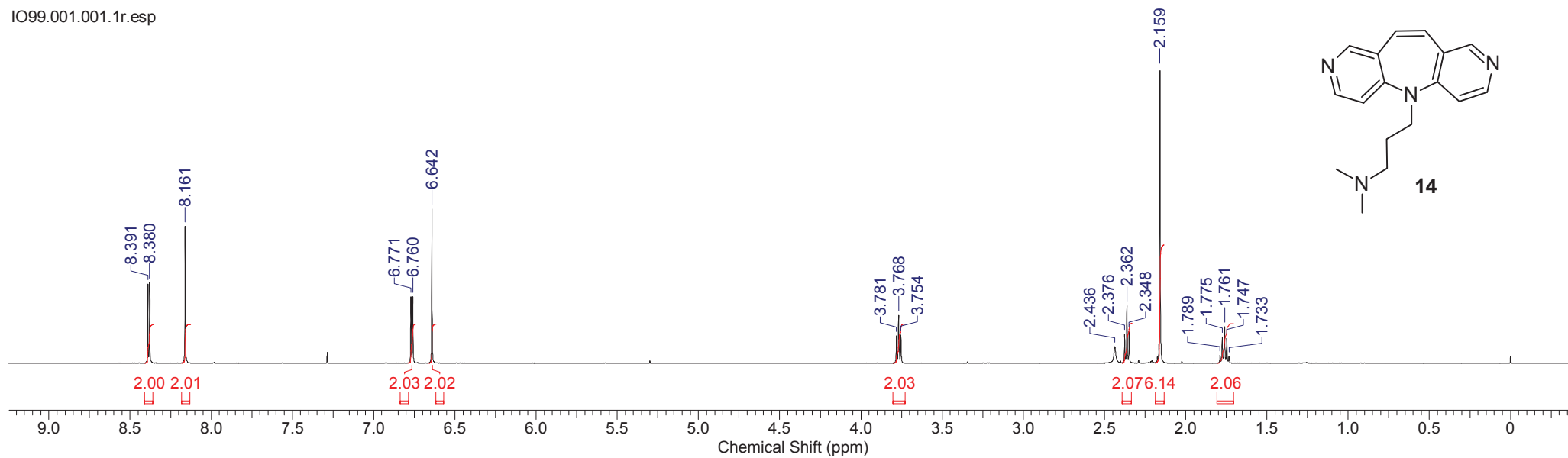


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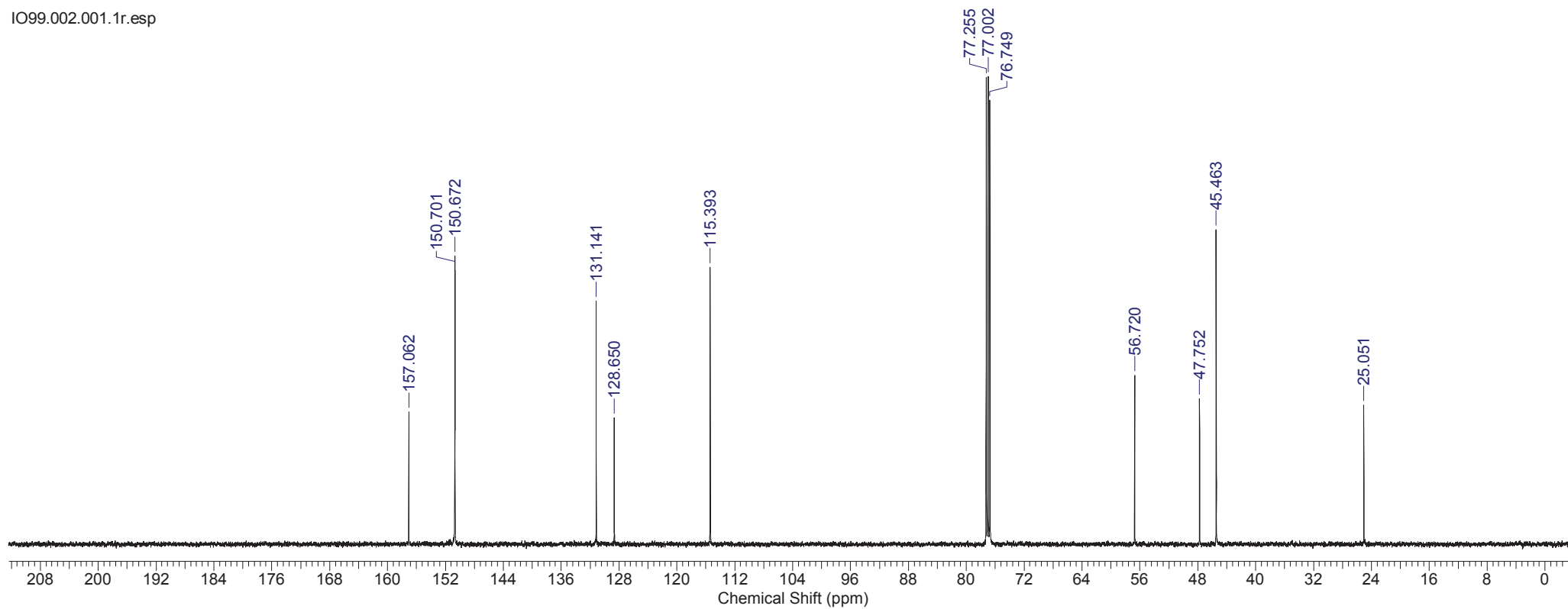




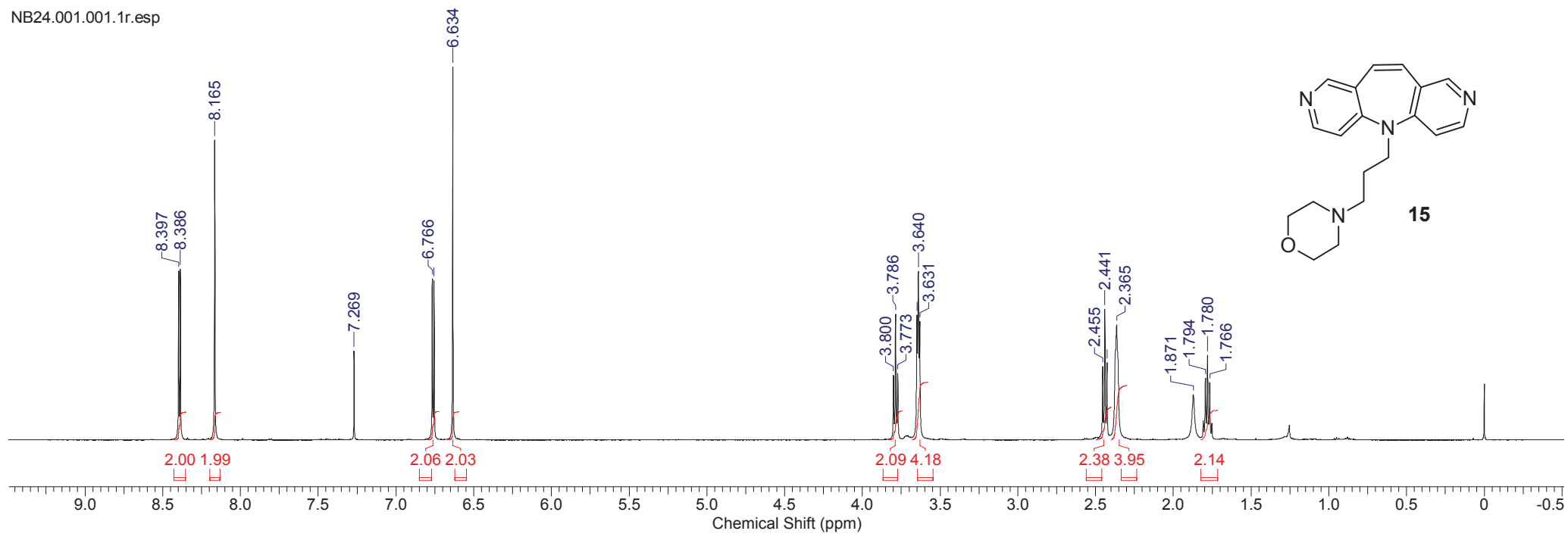
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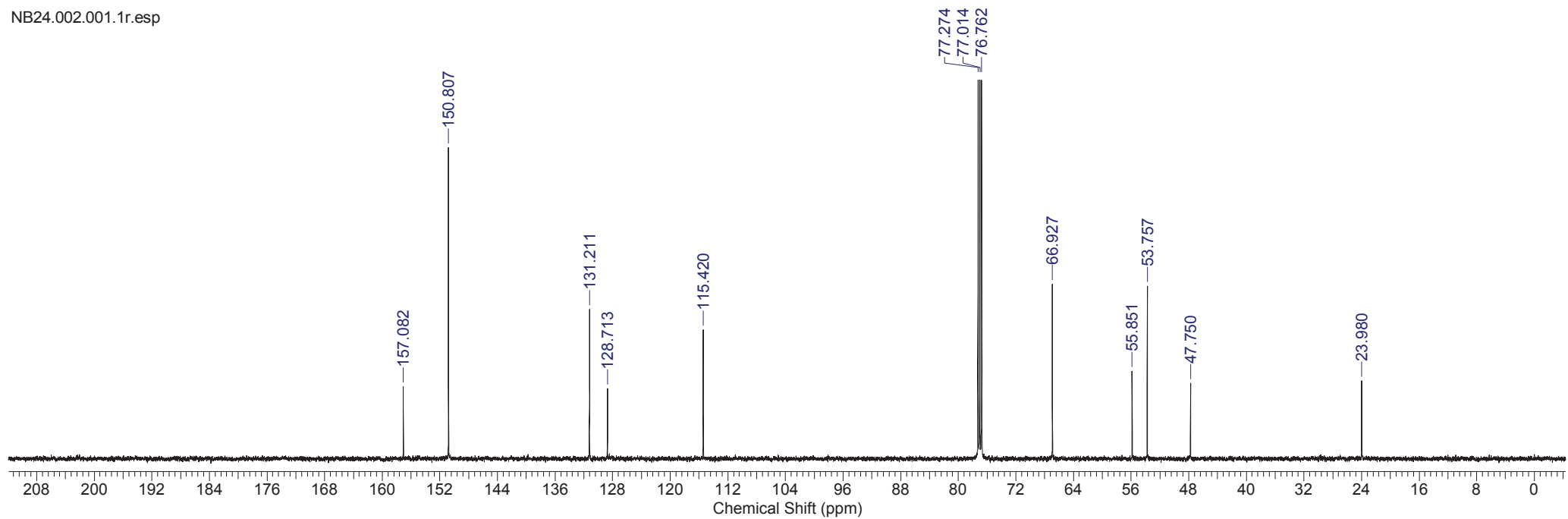
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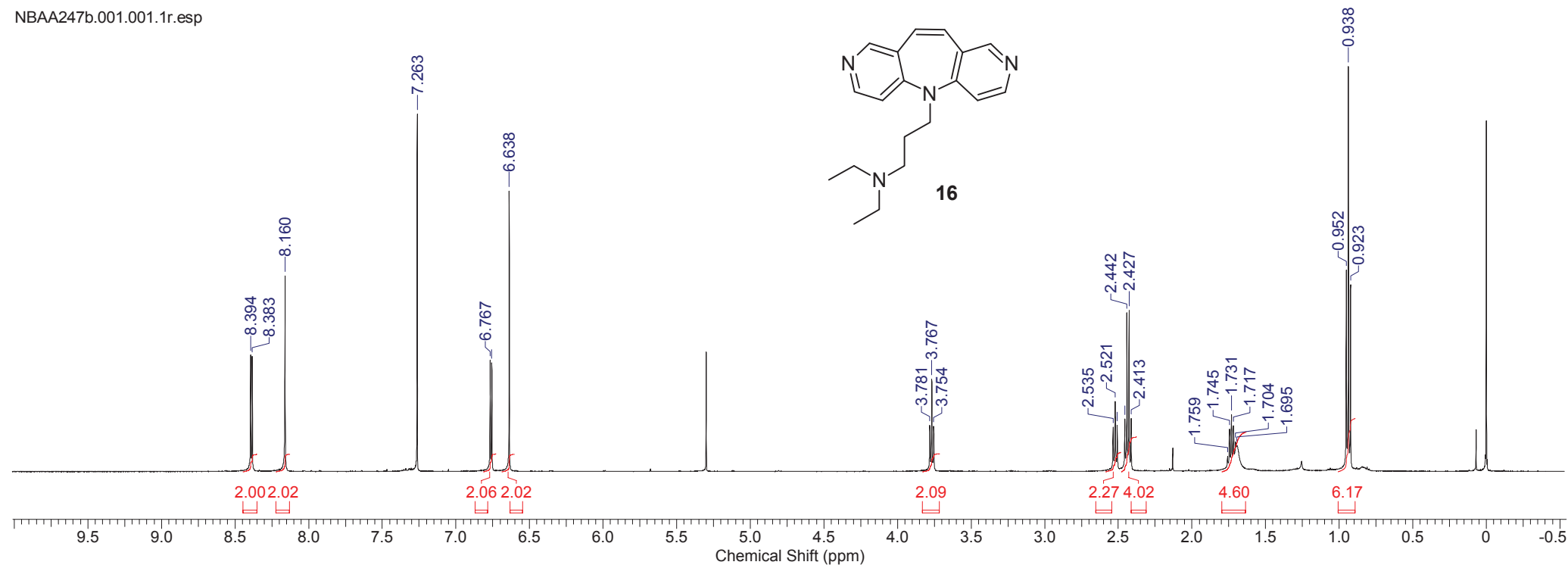
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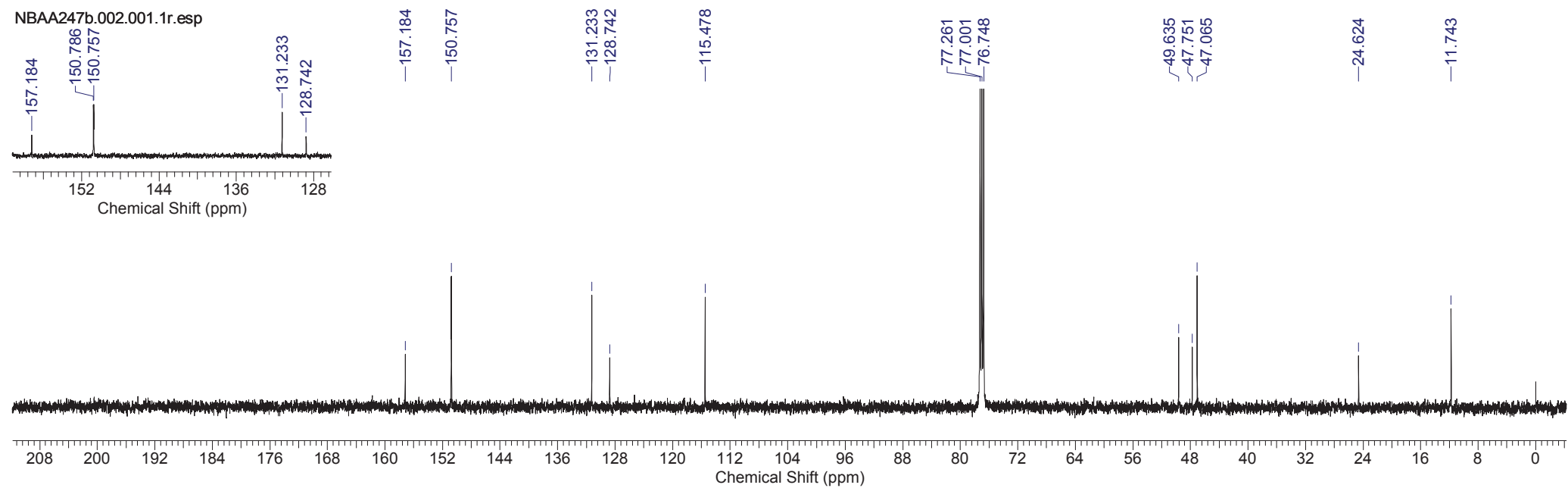
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NBAA247b.001.001.1r.esp

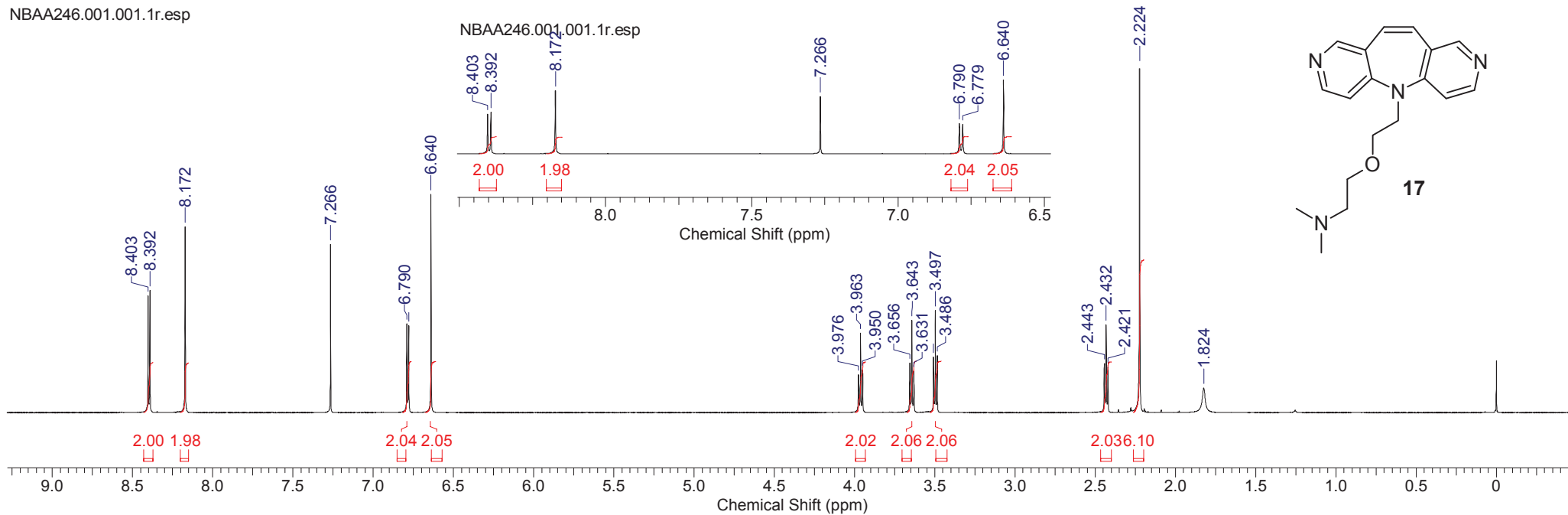


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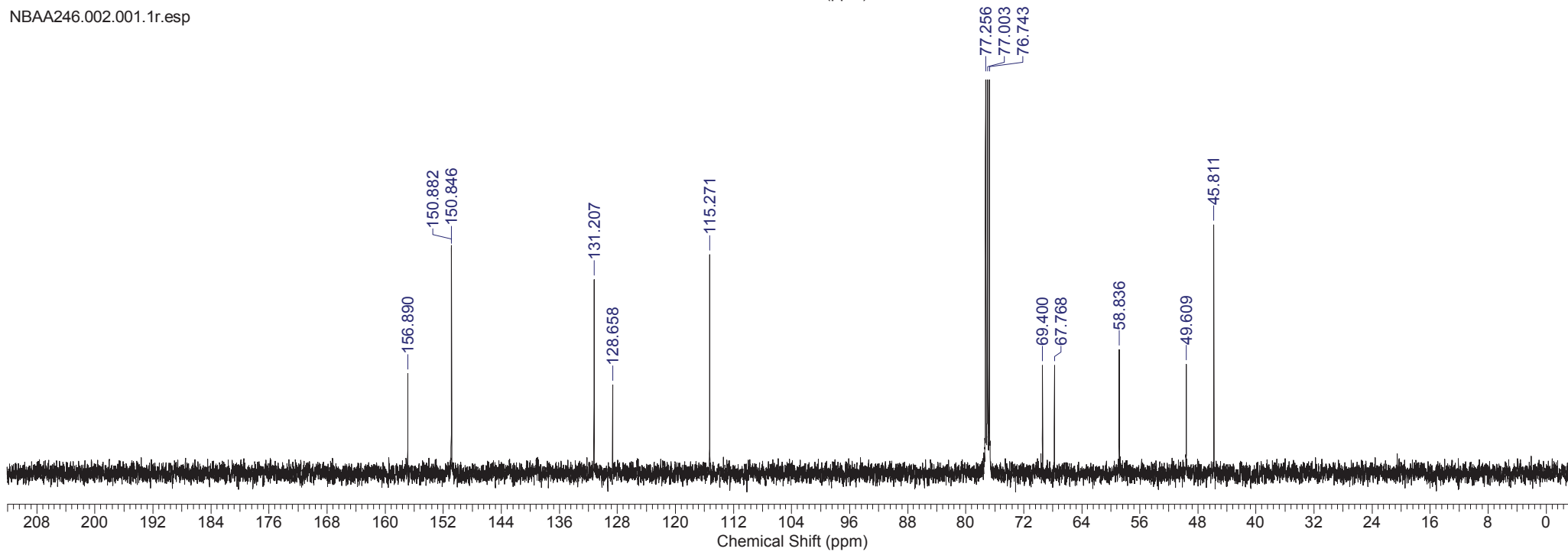


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NBAA246.001.001.1r.esp

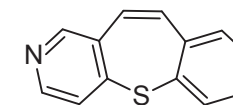


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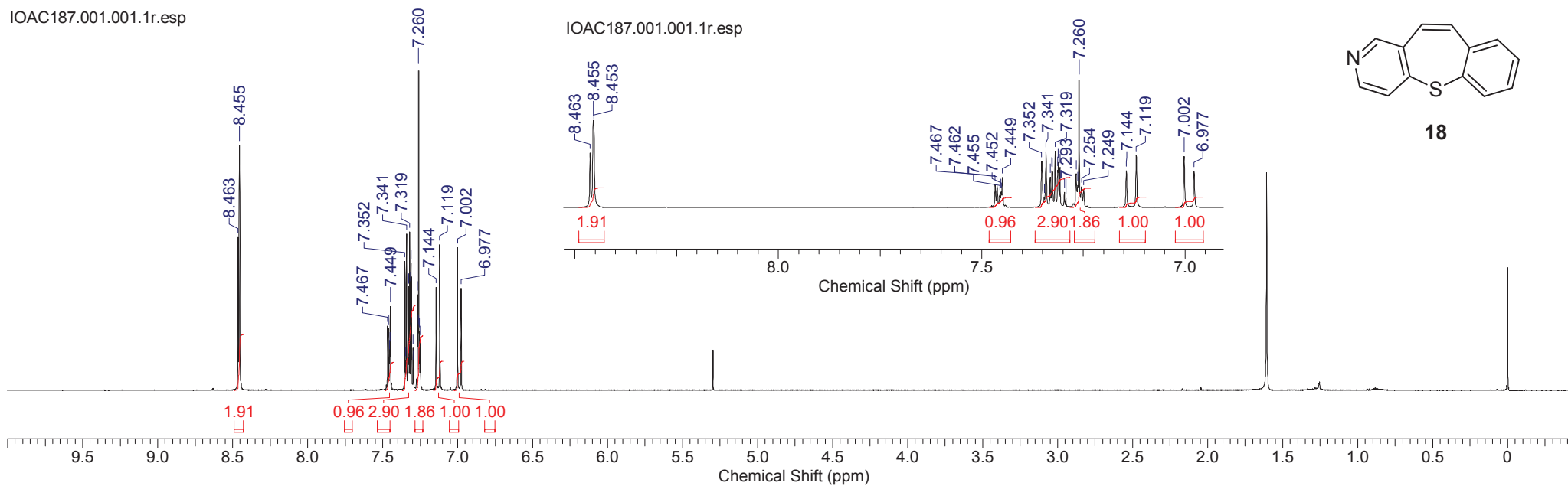


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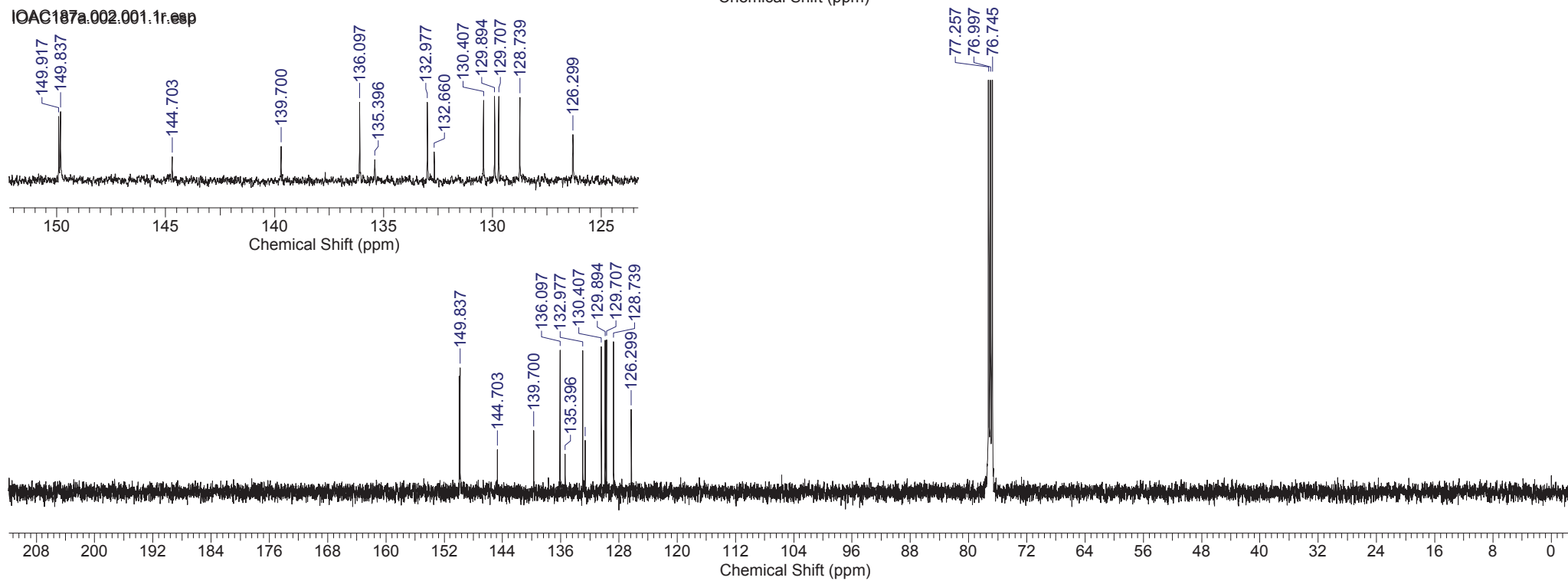
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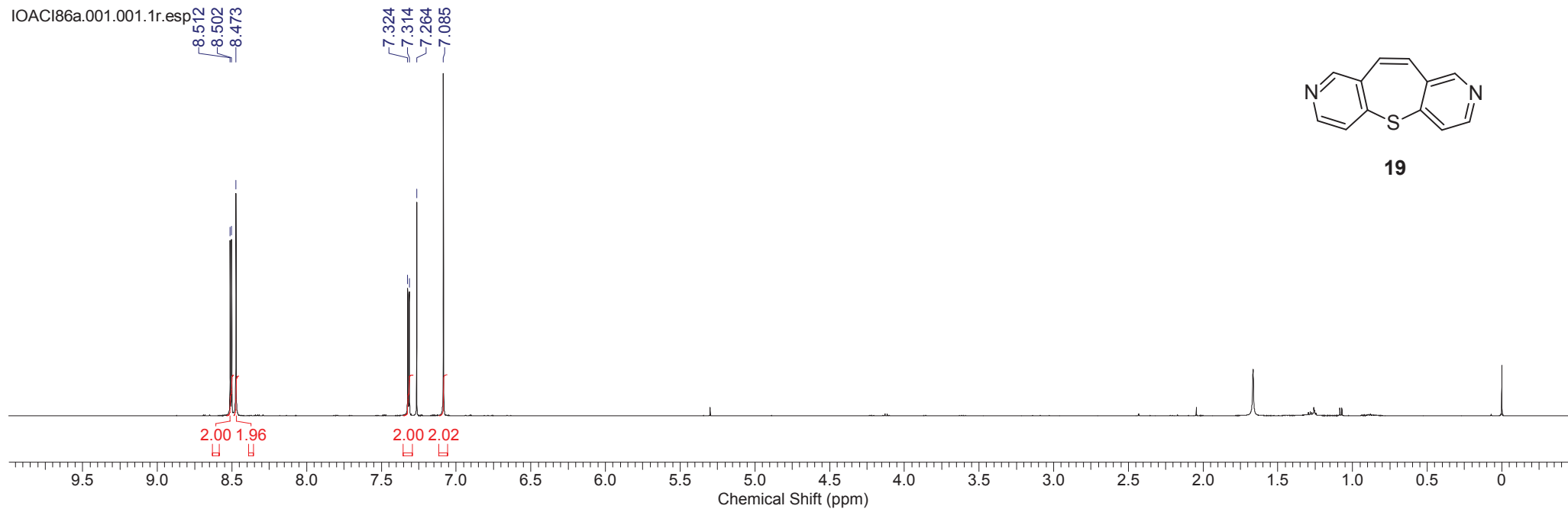
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IOAC187a.002.001.1r.esp



IOAC186a.001.001.1r.esp



IOAC186.002.001.1r.esp

